Report on the Deliberation Results

December 1, 2010

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Memary Tablets 5 mg, 10 mg, and 20 mg
[Non-proprietary name]	Memantine Hydrochloride (JAN*)
[Applicant]	Asubio Pharma Co., Ltd. (Currently Daiichi Sankyo Company, Limited)
[Date of application]	February 5, 2010

[Results of deliberation]
In the meeting held on November 24, 2010, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product, the re-examination period is 8 years, and the drug substance and the drug product are both classified as powerful drugs.

**Japanese Accepted Name (modified INN)*

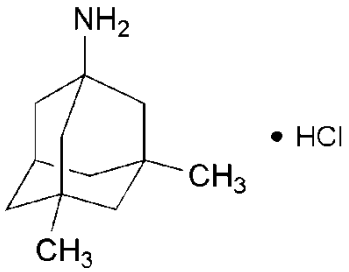
Review Report

November 12, 2010
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name]	Memary Tablets 5 mg, 10 mg, and 20 mg
[Non-proprietary name]	Memantine Hydrochloride
[Applicant]	Asubio Pharma Co., Ltd. (Currently Daiichi Sankyo Company, Limited)
[Date of application]	February 5, 2010
[Dosage form/Strength]	Film-coated tablets, each containing 5 mg, 10 mg, or 20 mg of memantine hydrochloride
[Application classification]	Prescription drug (1) Drug with a new active ingredient

[Chemical structure]



Molecular formula: $C_{12}H_{21}N \bullet HCl$

Molecular weight: 215.76

Chemical name: 3,5-Dimethyltricyclo[3.3.1.1^{3,7}]dec-1-ylamine monohydrochloride

[Items warranting special mention]	None
[Reviewing office]	Office of New Drug II

Review Results

November 12, 2010

[Brand name]	Memary Tablets 5 mg, 10 mg, and 20 mg
[Non-proprietary name]	Memantine Hydrochloride
[Applicant]	Asubio Pharma Co., Ltd. (Currently Daiichi Sankyo Company, Limited)
[Date of application]	February 5, 2010

[Results of review]

Based on the submitted data, it is concluded that the efficacy of the product in controlling the progression of dementia symptoms in patients with moderate to severe Alzheimer's disease has been demonstrated and its safety is acceptable in view of its observed benefits. The information on the efficacy and safety in patients with renal or hepatic impairment and in long-term use should be collected through the post-marketing surveillance, and the efficacy and safety of concomitant use of the product with donepezil hydrochloride should be investigated in the post-marketing clinical studies.

As a result of its regulatory review, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for the indication and dosage and administration as shown below.

[Indication]	Control of the progression of dementia symptoms in patients with moderate to severe Alzheimer's disease
[Dosage and administration]	The usual adult starting dose of memantine hydrochloride is 5 mg once daily orally. The dose should be titrated in weekly increments of 5 mg to the maintenance dose of 20 mg once daily.

Review Report (1)

October 15, 2010

I. Product Submitted for Registration

[Brand name]	Memary Tablets 5 mg, 10 mg, and 20 mg
[Non-proprietary name]	Memantine Hydrochloride
[Applicant]	Asubio Pharma Co., Ltd. (Currently Daiichi Sankyo Company, Limited)
[Date of application]	February 5, 2010
[Dosage form/Strength]	Film-coated tablets: Each tablet contains 5 mg, 10 mg, or 20 mg of memantine hydrochloride
[Proposed indication]	Control of the progression of dementia symptoms in moderate to severe Alzheimer's disease
[Proposed dosage and administration]	The usual adult starting dose of memantine hydrochloride is 5 mg once daily orally. The dose should be titrated in weekly increments of 5 mg to the maintenance dose of 20 mg once daily. The dose may be reduced according to the patient's condition.
[Items warranting special mention]	None

II. Summary of the Submitted Data and Outline of the Review by the Pharmaceuticals and Medical Devices Agency

A summary of the submitted data and an outline of the review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

1. Origin or history of discovery and usage conditions in foreign countries etc.

Merz + Co. GmbH & Co. (currently, Merz Pharmaceuticals GmbH; hereinafter referred to as "Merz") began development of memantine hydrochloride (hereinafter referred to as "memantine") in 19[redacted] as a drug with the primary action being promotion of dopamine release for the treatment of Parkinson's syndrome. Memantine has been approved and marketed in several countries and regions since 19[redacted] for all or some of the following indications: (1) Parkinson's syndrome, (2) mild to moderate brain dysfunction or dementia syndrome with symptoms such as impaired concentration or thinking, avolition, impaired activities of daily living, and depressed mood, and (3) cerebral or spinal spastic paralysis.

In 19[redacted], memantine was found to block glutamatergic *N*-methyl-D-aspartate (NMDA) receptor channels at approximately 0.01 times the concentration required to promote dopamine release. As an inhibitor of NMDA receptor channel activation, memantine was expected to reduce nerve cell toxicity and the impairment of long-term potentiation (LTP; a mechanism deeply involved in memory and learning) caused by excessive glutamate, thereby relieving symptoms of Alzheimer's disease (AD) such as impaired memory and learning.

In foreign countries, memantine had been developed by Merz since 19[redacted] and was first approved in Europe in May 2002 for the indication of treatment of "moderately severe to severe AD." As of September 2010, memantine (in tablet and liquid forms) has been approved in 70 countries, including the US and European countries, for the indication of treatment of "moderate to severe AD." The extended-release form of memantine was approved in the US in June 2010.

Its development in Japan was initiated by Suntory Co., Ltd. (Asubio Pharma Co., Ltd. at the time of filing of the application) in 19[redacted]. Based on the results of Japanese clinical studies and other data, the applicant has filed a marketing application of the product for the indication of "control of the progression of dementia symptoms in moderate to severe AD."

A request for an earlier approval of memantine was submitted in 2009 to the Ministry of Health, Labour and Welfare and PMDA by the Japanese Psychogeriatric Society, Japanese Society for Dementia Care, Japanese Society of Neurology, Japan Society for Dementia Research, and other organizations.

2. Physicochemical properties and specifications

2.A Summary of the submitted data

Memary Tablets (the drug product) are film-coated tablets, each containing 5, 10, or 20 mg of memantine (with a molecular formula of $C_{12}H_{21}N \cdot HCl$ and a molecular weight of 215.76).

2.A.(1) Drug substance

2.A.(1).1) Characterization

(a) Structure

The chemical structure of memantine has been elucidated by elemental analysis, chlorine content, mass spectrometry, infrared spectrophotometry (IR), hydrogen nuclear magnetic resonance spectrometry (^{1}H-NMR), carbon nuclear magnetic resonance spectrometry, and X-ray crystallography.

(b) General properties

The general properties of memantine, including color and shape, crystallinity, solubility, hygroscopicity, thermal analysis, pH, dissociation constant (pKa), partition coefficient, and crystalline polymorphism, have been determined. Memantine is a white crystalline powder. It is freely soluble in formic acid and ethanol (99.5), and soluble in water. Its mass increase due to moisture uptake is [redacted]% at [redacted]°C/[redacted]%RH, [redacted]% at [redacted]°C/[redacted]%RH, and [redacted]% at [redacted]°C/[redacted]%RH. Thermal analysis showed that memantine melts rather than sublimates. The pH of a solution of 0.1 g of memantine in 10 mL of water is 5.6. The pKa is 10.58. The partition coefficient between 1-octanol and a buffer solution of pH 1, 7, and 12 is 0.11, 0.32, and 1.49, respectively. X-ray powder diffraction showed that memantine is crystalline but does not exist in polymorphic forms.

2.A.(1).2) Manufacturing process

The drug substance is manufactured through the following 4 steps:

Step 1 [redacted].

Step 2 [redacted]

Step 3 [redacted]

Step 4 [redacted]

2.A.(1).3) Control of critical process steps

Steps [redacted] and [redacted] are defined as critical process steps. No in-process controls have been established.

2.A.(1).4) Control of drug substance

The proposed specifications for the drug substance include description (color, shape, solubility), identification (IR, qualitative test [chloride]), purity (heavy metals, related substances [gas chromatography (GC)]), loss on drying, residue on ignition, and content (potentiometric titration).

2.A.(1).5) Stability of drug substance

The following stability studies of the drug substance were conducted using batches manufactured on a commercial scale.

(a) Long-term testing (25˚C/60%RH, [redacted] polyethylene bag/fiber drum, 60 months)
(b) Accelerated testing (40˚C/75%RH, [redacted] polyethylene bag/fiber drum, 6 months)
(c) Stress testing, stability against temperature ([redacted]˚C, [redacted], [redacted] months)
(d) Stress testing, stability against temperature (60˚C, Petri dish [with glass cover], 6 months)
(e) Stress testing, stability against temperature ([redacted]˚C, [redacted], [redacted] months)
(f) Stress testing, stability against humidity (25˚C/90%RH, glass bottle [open], 6 months)
(g) Stress testing, stability against humidity ([redacted]˚C/[redacted]%RH, [redacted], [redacted] months)
(h) Stress testing, stability against humidity (40˚C/75%RH, glass bottle [open], 6 months)

(i) Stress testing, stability against humidity ([redacted]°C/[redacted]%RH, [redacted], [redacted] months)
(j) Stress testing, photostability (25°C/60%RH, Illuminant D_{65}, open Petri dish [exposed to light], [redacted] months)
(k) Stress testing, photostability (25°C/60%RH, Illuminant D_{65}, Petri dish/aluminum foil [protected from light], [redacted] months)
* Conditions for (j) and (k): An overall illumination of [redacted] lx·h; an integrated near ultraviolet energy of [redacted] W·h/m^2

Samples were tested for description (color, shape), [redacted], [redacted], related substances, loss on drying, and content (liquid chromatography [HPLC]) at all time points under the conditions for (a) to (k).

An increase in loss on drying was observed in the long-term testing (a), accelerated testing (b), and stress testing (f) to (i). There were no changes over time in any attributes in stress testing (c) to (e), (j), and (k).

Based on the above, a retest period of 5 years has been proposed for the drug substance when stored at room temperature.

2.A.(2) Reference standards or materials

The proposed specifications for the reference material include description (color, shape), identification (IR, ^{1}H-NMR), related substances (GC), loss on drying, and content (potentiometric titration).

2.A.(3) Drug product

2.A.(3).1) Description and composition of the drug product

The drug product comprises film-coated tablets (only 20 mg tablets have a score line), each of which contains the drug substance, excipients (lactose hydrate, microcrystalline cellulose), a disintegrator (low substituted hydroxypropylcellulose), a binder (hydroxypropylcellulose), a lubricant (magnesium stearate), coating agents (hypromellose, macrogol 6000, titanium oxide), a coloring agent (iron sesquioxide [for 5 mg tablets only]), and a glazing agent (carnauba wax).

2.A.(3).2) Pharmaceutical development

Since the commercial formulation developed by Merz contains an excipient ([redacted]) that has never been used in Japan, an original formulation was developed for the Japanese market. The proposed drug product is identical in formulation to those used in the Japanese late phase II study (Study IE2101) and subsequent studies.

2.A.(3).3) Manufacturing process

The manufacturing process for the drug product consists of the following 7 steps.

Step 1 (granulation process): [redacted]

[redacted]

Step 2 (drying process): [redacted]

Step 3 (sizing process): The dried granules are sized using a sizing machine.

Step 4 (mixing process): [redacted]

Step 5 (tableting process): Using a rotary tablet machine, the granules for tableting are compressed and molded into uncoated tablets.

Step 6 (coating process): [redacted]

The uncoated tablets are sprayed with the coating solution, dried, and then glazed by applying carnauba wax.

Step 7 (labeling and packaging process):

(a) Press through package (PTP)/aluminum pillow package: Polypropylene film is molded at a high temperature in a PTP packaging machine, and after loading the tablets, is heat-sealed with aluminum foil. The sealed products are cut into PTP sheets. The PTP sheets are sealed in aluminum/polyethylene laminated film and made into pillow packages, which are placed into paper boxes.

(b) Plastic bottle package: The tablets are placed in a polyethylene bottle, which is sealed with a polyethylene cap. A label is placed on the bottle.

Steps [redacted] and [redacted] are defined as critical process steps, and control parameters and control values are specified for Steps [redacted], [redacted], [redacted], [redacted], and [redacted].

2.A.(3).4) Control of drug product

The proposed specifications for the drug product include description (color, shape), identification (fluorescence reaction), related substances (HPLC), uniformity of dosage units (content uniformity testing by HPLC), dissolution (dissolution testing by HPLC), and content (HPLC).

2.A.(3).5) Stability of drug product

The following stability studies were conducted using batches manufactured on a pilot scale.

(a) Long-term testing (25˚C/60%RH, PTP/aluminum pillow package, 36 months)
(b) Long-term testing (25˚C/60%RH, plastic bottle package, 36 months)

(c) Intermediate testing (30˚C/65%RH, PTP/aluminum pillow package, 12 months)
(d) Intermediate testing (30˚C/65%RH, plastic bottle package, 12 months)
(e) Accelerated testing (40˚C/75%RH, PTP/aluminum pillow package, 6 months)
(f) Accelerated testing (40˚C/75%RH, plastic bottle package, 6 months)
(g) Stress testing, stability against temperature (60˚C, open Petri dish, [redacted] months)
(h) Stress testing, stability against humidity (25˚C/90%RH, open Petri dish, 3 months)
(i) Stress testing, photostability (Illuminant D_{65}, open Petri dish [exposed to light], [redacted] months)
(j) Stress testing, photostability (Illuminant D_{65}, Petri dish/aluminum foil [protected from light], [redacted] months)
* Conditions for (i) and (j): An overall illumination of ≥1.2 million lx·h, an integrated near ultraviolet energy of ≥200 W·h/m^2

Samples were tested for description, related substances, water content, dissolution, hardness, and content at all time points under the conditions for (a) to (j), for uniformity of dosage units at 0, [redacted], and 36 months of storage under the conditions for (a) and (b), and for microbial limits at 0, [redacted], and 36 months of storage under the conditions for (a) and (b).

An increase in related substances was observed in the 5, 10, and 20 mg tablets of the drug product in long-term testing (a) and (b), intermediate testing (c) and (d), accelerated testing (e) and (f), and stress testing (g), and the 5 and 20 mg tablets failed to meet the specifications for accelerated testing (e) and (f). [redacted] No changes were observed in stress testing (j).

Based on the above, a shelf-life of 36 months has been proposed for the drug product when stored at room temperature in a PTP sheet within an aluminum pillow package or in a plastic bottle.

2.B Outline of the review by PMDA

To PMDA's question about the solvent used in the manufacturing process for Starting Material A, the applicant responded that Solvent A, a Class 1 solvent according to the "Guideline for Residual Solvents" (PMSB/ELD Notification No. 307 dated March 30, 1998; ICH-Q3C), is used by [redacted] of [redacted] suppliers of Starting Material A. Accordingly, PMDA instructed the applicant not to use Starting Material A manufactured using this solvent for manufacturing the drug substance.

The applicant explained as follows:
Since the drug substance is distributed globally and the supply of the drug substance should be ensured, it is impossible to obtain Starting Material A manufactured without using Solvent A exclusively for Japan. The level of Solvent A in Starting Material A manufactured using this solvent will be controlled by specifying a residual solvent limit of <[redacted] ppm (stricter than [redacted] ppm prescribed by ICH-Q3C).

PMDA accepted the above response, and considers that there are no particular problems with regard to the quality of the drug product.

3. Non-clinical data

3.(i) Summary of pharmacology studies

3.(i).A Summary of the submitted data

3.(i).A.(1) Primary pharmacodynamics

3.(i).A.(1).1) Effects on NMDA receptor

(a) Affinity for NMDA receptor channels (4.2.1.1.1)

Using the membrane fraction of cerebral cortical neurons from male SD rats (n = 2), the affinity of memantine for NMDA receptor channels was evaluated based on its ability to replace tritium-labeled MK-801 (^{3}H-MK-801, 5 nmol/L) bound to the phenyl-cyclohexyl-piperidine (PCP) binding site in the NMDA receptor channel in the presence of glutamate (10 μmol/L) and glycine (10 μmol/L). Memantine reduced the binding of ^{3}H-MK-801 to NMDA receptor channels with a half maximal inhibitory concentration (IC_{50}) of 1.47 μmol/L and an inhibition constant (K_i) of 0.67 μmol/L.

(b) Affinity for various receptors (4.2.1.1.2)

Specific binding of labeled ligands to 61 receptors and transporters were challenged by memantine (10 μmol/L) to determine its ability to replace the ligands. Replacement was 91.08% at the PCP-binding site of the NMDA receptor channel, and was up to 44.98% for the other 60 receptors and transporters.

(c) Activity to block NMDA receptor channels (4.2.1.1.3)

Hippocampal neurons prepared from rat fetuses (embryonic day 20 to 21) were cultured for 12 to 15 days and then cumulatively exposed to memantine at 0.3, 1.0, 3.0, 10, and 30 μmol/L. The NMDA (200 μmol/L) -induced currents in the presence of D-serine (10 μmol/L) were measured at a fixed membrane potential of −70 mV using the whole-cell patch clamp technique. Memantine blocked NMDA-induced currents in a concentration-dependent manner with an IC_{50} value of 1.56 ± 0.09 μmol/L (mean ± standard deviation [SD]; n = 9). Meanwhile, currents induced by α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA, 100 μmol/L) or γ-aminobutyric acid (GABA, 10 μmol/L) were not blocked by memantine at concentrations of up to 30 μmol/L. The on-rate of inhibition of NMDA-induced currents ($1/\tau_{on}$) was dependent on the concentration of memantine, while the off-rate ($1/\tau_{off}$) was constant regardless of memantine concentration. The on- and off-rates around the IC_{50} (1 μmol/L) of memantine ($1/\tau_{on} = 0.27$ sec^{-1}, $1/\tau_{off} = 0.19$ sec^{-1}) were greater than those estimated at the IC_{50} (0.14 μmol/L) of MK-801 ($1/\tau_{on} = 0.029$ sec^{-1}, $1/\tau_{off} = 0.005$ sec^{-1}; Parsons CG, et al. *Neuropharmacology*. 1995;34:1239-1258). The inhibitory effects of memantine (10 μmol/L) on NMDA (200 μmol/L) -induced currents in the presence of D-serine (10 μmol/L) were evaluated at various constant membrane potentials between −80 mV and +60 mV. The results revealed that the activity of memantine to block NMDA receptor channels was decreased at shallower membrane potentials.

3.(i).A.(1).2) Effects on impairment of synaptic plasticity

(a) Effects in model of low magnesium-induced impairment of long-term potentiation (4.2.1.1.4)

Hippocampal slice samples isolated from male SD rats (n = 6-7) were exposed to memantine (1, 10, or 30 μmol/L), MK-801 (0.01, 0.1, or 1 μmol/L), or vehicle, and were preincubated for at least 7 hours. Then the concentration of magnesium (Mg^{2+}) in the perfusion fluid was reduced from 1 mmol/L to 10 μmol/L (low-Mg^{2+} perfusion), which was followed by tetanic stimulation 60 minutes later. The effects of memantine and MK-801 on the low-Mg^{2+}-induced impairment of long-term potentiation (LTP) formation were evaluated based on the mean initial slope of the field excitatory postsynaptic potential (fEPSP) measured during the 30-minute period before low-Mg^{2+} perfusion, at 45 to 60 minutes after reduction of Mg^{2+} concentration, and at 30 to 60 minutes after tetanic stimulation. In samples treated with vehicle, the increase in the fEPSP slope at 45 to 60 minutes after low- Mg^{2+} perfusion was 87.2% ± 10.6% (mean ± SD) relative to before low-Mg^{2+} perfusion, while a decrease of 4.1% ± 9.8% in the fEPSP slope after tetanic stimulation was observed relative to before tetanic stimulation. In samples treated with memantine at 1, 10, and 30 μmol/L, increases of 84.1% ± 11.6%, 30.1% ± 4.9%, and 32.8% ± 7.4%, respectively, in the fEPSP slope after low-Mg^{2+} perfusion were observed relative to before low-Mg^{2+} perfusion, showing that low Mg^{2+}-induced fEPSP enhancement was reduced by memantine at 10 and 30 μmol/L, while increases of 43.4% ± 8.4%, 61.5% ± 5.3%, and 14.9% ± 2.8%, respectively, in the fEPSP slope after tetanic stimulation were observed relative to before tetanic stimulation, showing that impairment of LTP was reduced by memantine at 1 and 10 μmol/L. In samples treated with MK-801 at 0.01, 0.1, and 1 μmol/L, the increasing rate of the fEPSP slope after low-Mg^{2+} perfusion decreased relative to before low-Mg^{2+} perfusion in a concentration-dependent manner, while after tetanic stimulation, the fEPSP slope did not increase at any concentration of MK-801.

The applicant interpreted the above results as demonstrating the capacity of memantine to reduce low Mg^{2+}-induced impairment of LTP.

(b) Activity to reduce NMDA-induced learning impairment (4.2.1.1.5)

Male SD rats (160-180 g or 200-220 g; n = 8-16) were trained using a passive avoidance learning device consisting of 3 compartments (starting, light, and dark compartments). A memory retention test was performed at 24 hours after training. In the retention test, passive avoidance memory was assessed in terms of the latency time taken to leave the starting compartment and the time to enter the dark compartment. Passive avoidance learning was impaired in a dose-dependent manner by intraperitoneal administration of NMDA at 12.5, 25, or 50 mg/kg at 30 minutes before training, but not by intraperitoneal administration of NMDA at 25 mg/kg at 24 hours before training. Then, vehicle or memantine at 2.5, 5.0, or 10 mg/kg was administrated by intraperitoneal injection concomitantly with 25 mg/kg of NMDA at 30 minutes before training. Impairment of passive avoidance learning was significantly reduced by administration of memantine at 2.5 or 5 mg/kg but not at 10 mg/kg.

Based on the above results, the applicant considers that learning impairment induced by intraperitoneal administration of NMDA is not related to neuronal damage, and that memantine reduces NMDA-induced impairment of passive avoidance learning, which is not considered attributable to neuronal

damage.

3.(i).A.(1).3) Effects on neuronal damage

(a) Effects on neuronal damage induced by a combination of amyloid beta 25-35 and glutamate (4.2.1.1.6)

Cerebral cortical neurons prepared from Wistar rat fetuses on embryonic day 18 were cultured for 7 days, spiked with amyloid beta 25-35 ($A\beta_{25-35}$, 1 μmol/L) or vehicle, cultured for 2 additional days, then spiked with glutamate (50 μmol/L) or vehicle, and cultured for 1 more day. The severity of neuronal damage was assessed based on the cell survival rate (MTT assay) calculated on a scale from 0% to 100%, defined as the rate in the $A\beta_{25-35}$ + glutamate group and the rate in the vehicle group, respectively. The mean cell survival rate was 94% in the $A\beta_{25-35}$ group (spiked with $A\beta_{25-35}$ alone) and 83% in the glutamate group (spiked with glutamate alone). The mean cell survival rates (n = 8) after exposure to memantine at 0.1, 0.3, 1.0, and 3.0 μmol/L immediately before glutamate spike were 41%, 71%, 111%, and 99%, respectively, and after exposure to MK-801 at 0.001, 0.003, 0.01, and 0.03 μmol/L in the same manner, the rates (n = 8) were 65%, 71%, 85%, and 97%, respectively. Both memantine and MK-801 inhibited neuronal damage in a concentration-dependent manner with IC_{50} values of 0.13 and 0.0004 μmol/L, respectively.

(b) Activity to reduce learning impairment in rat model by bilateral intrahippocampal injection of $A\beta_{1-40}$ and ibotenic acid (4.2.1.1.7, 4.2.1.1.8, 4.2.1.1.9)

$A\beta_{1-40}$ (4 μg/μL, 1 μL) was bilaterally injected into 4 hippocampal sites (2 sites on each side) of 10-week-old male F344 rats (n = 8-14), and ibotenic acid (0.6 μg/μL, 0.5 μL) was also injected into the same sites 2 days later. The rats were tested in the water maze task (acquisition trials, 4 trials/day for 4 days; exploration trials, once at 2 hours after the completion of each acquisition trial) starting at 5 weeks after injection of $A\beta_{1-40}$. Neuronal damage was evaluated based on the level of specific binding of ^{3}H-PK11195 to peripheral-type benzodiazepine binding sites (PTBBS; a gliosis marker that increases with neuronal damage) in a crude hippocampal membrane fraction collected on the day following completion of the learning experiment (PTBBS level). The acquisition and exploration trials evaluated the time required to reach the platform by swimming (escape latency) and the frequency of crossing over the previous platform location. Compared with rats that received normal saline in both hippocampi (the pseudo-surgery group), rats that had continuously received vehicle subcutaneously for 6 weeks starting at 24 hours before the injection of $A\beta_{1-40}$ (the vehicle group) showed a significant prolongation of escape latency in the acquisition trials and a significant decrease in frequency of crossing the previous platform location in the exploration trials. Moreover, the PTBBS level was higher in the vehicle group than in the pseudo-surgery group, suggesting that injection of $A\beta_{1-40}$ and ibotenic acid had induced neuronal damage. A 6-week continuous subcutaneous infusion of memantine at 10 or 20 mg/kg/day starting at 24 hours before the $A\beta_{1-40}$ injection reduced the prolongation of escape latency shown in the vehicle group in the acquisition trials and inhibited the reduction of the frequency of crossing the previous platform location in the exploration trials, and reduced the increase in the PTBBS level seen in the vehicle group. Administration of memantine (5 mg/kg/day) did not affect the prolongation of escape

latency, the frequency of crossingthe previous platform location, or the increase in the PTBBS level.

MK-801 was also administered at 0.312, 0.624, or 1.248 mg/kg/day by continuous subcutaneous infusion for 6 weeks starting at 24 hours before the $A\beta_{1-40}$ injection. The results showed MK-801 at 0.312 mg/kg/day did not affect the prolongation of escape latency, the decrease in frequency of crossing the previous platform location, or the increase in the PTBBS level observed in the vehicle group. MK-801 at 0.624 mg/kg/day reduced the increase in the PTBBS level, but did not affect the reduced frequency of crossing the previous platform location observed in the vehicle group, and showed a greater prolongation of escape latency than that in the vehicle group. All the rats receiving MK-801 at 1.248 mg/kg/day died within 10 days after administration.

Based on the above results, the applicant discussed that, in the rat model of water maze learning impairment by bilateral intrahippocampal injection of $A\beta_{1-40}$ and ibotenic acid, continuous subcutaneous infusion of memantine at 10 or 20 mg/kg/day reduced learning impairment, that this was likely attributable to the neuronal protection effects of memantine, and that MK-801, albeit showing neuronal protection effects at 0.624 mg/kg/day, exacerbated learning impairment.

(c) Effects on memory/learning ability in normal rats (4.2.1.1.10)

Ten-week-old male F344 rats (n = 12-13) received a 10-day continuous subcutaneous infusion of memantine at 20 mg/kg/day, MK-801 at 0.624 mg/kg/day, or vehicle, and were tested in the water maze task starting on Day 7 in a manner similar to that in Section (b) above. In the acquisition trials, escape latency decreased over time in both the vehicle and memantine groups, but was significantly prolonged in the MK-801 group in comparison with the vehicle group. In the exploration trials, the frequency of crossing the previous platform location did not differ between the memantine group and the vehicle group, but was lower in the MK-801 group than in the vehicle group.

Based on the above results, the applicant discussed that memantine did not affect water maze learning in normal rats at dose levels required for its protective effects against neuronal damage caused by $A\beta_{1-40}$ and ibotenic acid, while MK-801 induced learning impairment.

3.(i).A.(1).4) Pharmacodynamics of metabolites

(a) Affinity of memantine metabolites for NMDA receptor channels (4.2.1.1.1)

Using the membrane fractions of cerebral cortical neurons from male SD rats, the affinity of [redacted] different memantine metabolites for NMDA receptor channels was evaluated by the method similar to the one described in 3.(i).A.(1).1).(a). [redacted]

(b) Ability of memantine metabolites to block NMDA receptor channels (4.2.1.1.11)

[redacted]

[redacted]

3.(i).A.(2) Secondary pharmacodynamics

No data submitted.

3.(i).A.(3) Safety pharmacology

3.(i).A.(3).1) Effects on general symptoms and behavior and central nervous system (4.2.1.3.1, 4.2.1.3.2)

(a) Effects on general symptoms and behavior in mice

A single dose of memantine (10, 30, or 100 mg/kg) or vehicle was orally administered to female Naval Medical Research Institute (NMRI) mice (18-22 g; n = 8), and effects of memantine on general symptoms and behavior were monitored (Irwin's test). A slight decrease in postural reaction was observed in the ≥30 mg/kg groups. In addition, stereotypy, Straub tail reaction, tremor, abnormal posture, gait ataxia, and a decrease or inhibition of reactivity, touch/pain response, startle response, ipsilateral flexor reflex, righting reflex, and grip strength were observed in the 100 mg/kg group.

(b) Effects on spontaneous motor activity in mice

A single dose of memantine (5, 15, or 50 mg/kg) or vehicle was orally administered to female NMRI mice (18-23 g; n = 10). Locomotor activity increased in the memantine ≥5 mg/kg groups.

(c) Effects on hexobarbital-induced sleep time in mice

At 60 minutes after a single oral dose of memantine (15, 30, or 60 mg/kg) or vehicle to male and female NMRI mice (20-24 g; n = 5 per sex), hexobarbital was administered intravenously. Hexobarbital-induced sleep time was prolonged in the memantine ≥30 mg/kg groups.

(d) Effects on electric shock-induced convulsions in mice

At 60 minutes after a single oral dose of memantine (10, 15, 22, or 33 mg/kg) or vehicle to female NMRI mice (18-23 g; n = 5), an electric shock (45 mA; 0.7 second) was given to the animals. Memantine exhibited anticonvulsant activity in a dose-dependent manner (median effective dose [ED_{50}] = 18.4 mg/kg).

At 60 minutes after a single oral dose of memantine (10, 30, or 100 mg/kg) or vehicle to female NMRI mice (19-23 g; n = 5), an electric shock (5 mA; 0.8 second) below the convulsive threshold was given to the animals. No convulsions were observed in the memantine groups.

(e) Effects on pentetrazol-induced convulsions in mice

At 60 minutes after a single oral dose of memantine (10, 15, 22, or 33 mg/kg) or vehicle to female NMRI mice (19-23 g; n = 5), pentetrazol (110 mg/kg) was administered subcutaneously. No anticonvulsant response was observed in the memantine groups. A significant increase in the incidence of convulsions was observed in the memantine ≥22 mg/kg groups compared with the vehicle group.

At 60 minutes after a single oral dose of memantine (10, 30, or 100 mg/kg) or vehicle to female NMRI mice (19-23 g; n = 10), pentetrazol was administered subcutaneously at 50 mg/kg (a dose level not inducing convulsions). Memantine induced convulsions in a dose-dependent manner (ED_{50} = 17.8 mg/kg).

(f) Effects on acetic acid-induced writhing response in mice (pain response)

At 60 minutes after a single oral dose of memantine (10, 30, or 100 mg/kg) or vehicle to female NMRI mice (n = 10), a 1% acetic acid solution was administered intraperitoneally at 10 mL/kg. Memantine inhibited the acetic acid-induced writhing response in a dose-dependent manner (ED_{50} = 44.9 mg/kg).

(g) Effects on thermal stimulation in mice

At 30 and 60 minutes after a single oral dose of memantine (10, 20, or 40 mg/kg) or vehicle to female SD rats (158-184 g; n = 10), thermal stimulation was applied to the tail of the animals. No effects on pain response time were observed in any of the memantine groups

(h) Effects on body temperature in mice

At 60 minutes after a single oral dose of memantine (10, 30, or 100 mg/kg) or vehicle to female NMRI mice (18-22 g; n = 8), reserpine (5 mg/kg) was administered intraperitoneally. Memantine inhibited the reserpine-induced decrease in body temperature in animals treated at ≥10 mg/kg.

3.(i).A.(3).2) Effects on cardiovascular and respiratory systems (4.2.1.3.1, 4.2.1.3.2, 4.2.1.3.3, 4.2.1.3.4, 4.2.1.3.5, 4.2.1.3.6)

(a) *In vitro* study

CHO cells expressing human ether-a-go-go related gene (hERG) K^+ channels were exposed to memantine (10, 30, or 100 µmol/L). At 100 µmol/L (120-fold the mean plasma concentration [0.83 µmol/L] after multiple doses of 20 mg of memantine in humans), memantine reduced the change in membrane potential and K^+ channel currents by 29% and 15%, respectively.

(b) *In vivo* studies

Female beagle dogs (11.7-12.8 kg; n = 5) received single escalating intraduodenal doses of memantine at 0 (vehicle) and 3, 10, and 30 mg/kg. As a result, cardiac output and stroke volume decreased after administration of memantine at ≥10 mg/kg, and left ventricular systolic pressure decreased at 30 mg/kg. All the decreases noted were statistically significant in comparison with the levels after vehicle administration. However, no changes were observed in peripheral arterial pressure, pulmonary arterial pressure, pulmonary arterial wedge pressure, heart rate, maximum rate of left ventricular pressure rise

(LV dP/dt max), central venous pressure, oxygen tension in the blood, or blood pH. Noradrenaline (2 μg/kg) and isoproterenol (2 μg/kg) were intravenously administered before vehicle administration and after data collection at the final dose of memantine. Memantine did not influence the effects of noradrenaline and isoproterenol on blood pressure and heart rate.

Male and female beagle dogs (6.7-11.5 kg; n = 4 per sex) orally received a blank control (empty capsule only) or memantine for 28 days at a daily dose escalated every 7 days from 0.3 to 3.0, 6.0, and 10 mg/kg, and blood pressure, heart rate, and ECG parameters (PR, RR, QRS, and QT intervals) were continuously measured by telemetry. A dose-dependent increase in heart rate was observed in male dogs after administration of memantine at 6.0 and 10 mg/kg, but there were no significant differences between these dogs and the control animals. Memantine did not affect blood pressure, ECG parameters, clinical observations, or body weight.

3.(i).A.(3).3) Effects on autonomic nervous system/smooth muscles (4.2.1.3.1, 4.2.1.3.2)

The contractile response of the ileum isolated from female Hartley guinea pigs (388-510 g; n = 6) was evaluated following exposure to memantine (1×10^{-9} to 1×10^{-3} g/mL [4.6 nmol/L to 4.6 mmol/L]). Contraction was observed after exposure to memantine at $\geq 1 \times 10^{-5}$ g/mL (46 μmol/L), and reached the peak (equivalent to 26% of the contraction induced by acetylcholine [ACh] at 5×10^{-7} g/mL) at 1×10^{-4} g/mL (460 μmol/L), but decreased (equivalent to 9% of the contraction induced by Ach at 5×10^{-7} g/mL) at 1×10^{-3} g/mL (4.6 mmol/L). Memantine-induced contraction was not inhibited by papaverine (3×10^{-5} g/mL), antazoline (3×10^{-8} g/mL), or atropine (3×10^{-8} g/mL). Meanwhile, memantine at $\geq 1 \times 10^{-5}$ g/mL (46 μmol/L) showed a concentration-dependent inhibition of contraction induced by ACh (5×10^{-7} g/mL), histamine (5×10^{-8} g/mL), barium chloride (2×10^{-4} g/mL), or serotonin (1.5×10^{-8} g/mL).

3.(i).A.(3).4) Effects on gastrointestinal system (4.2.1.3.1, 4.2.1.3.2)

At 1 hour after an oral dose of memantine (10, 20, or 40 mg/kg) or vehicle to female SD rats (n = 10), a solution of a mixture of 10% charcoal powder and 5% powdered acacia (10 mL/kg) was administered orally. Gastrointestinal propulsion was evaluated by examining the presence of charcoal in the cecum at 3 hours after administration of the mixed solution, and the results showed that memantine inhibits gastrointestinal propulsion with an ED_{50} of approximately 20 mg/kg.

3.(i).A.(3).5) Effects on urine output/urinary electrolyte excretion (4.2.1.3.1, 4.2.1.3.2)

Memantine (10, 20, or 40 mg/kg), furosemide (20 mg/kg), or vehicle was orally administered to female SD rats (158-186 g; n = 10), and urine was collected up to 24 hours post-dose. In cumulative urine samples for the periods from 0 to 2, from 0 to 3, from 0 to 4, and from 0 to 5 hours post-dose, the total amounts of excreted Na^+ and Cl^- in the memantine ≥20 mg/kg groups and the urine output in the memantine 40 mg/kg group were significantly larger than those in the vehicle group, while there were no effects on the amount of excreted K^+. Cumulative urine samples for the period from 0 to 24 hours post-dose showed no changes in any parameters. In the furosemide group, the amounts of excreted Na^+,

K^+, and Cl^- for the periods from 0 to 1, from 0 to 2, from 0 to 3, from 0 to 4, and from 0 to 5 hours post-dose were significantly larger than those in the vehicle group, while cumulative urine samples for the period from 0 to 24 hours post-dose showed no changes in any parameters.

3.(i).A.(4) Pharmacodynamic drug interactions

No data submitted.

3.(i).B Outline of the review by PMDA

3.(i).B.(1) Effects of memantine at higher doses

PMDA asked the applicant to explain the reasons why low Mg^{2+}-induced impairment of LTP was not reduced at a high concentration (30 μmol/L) of memantine, and why NMDA-induced learning impairment was not reversed in the high-dose (10 mg/kg) treatment group.

The applicant response is presented in the two sections below.

3.(i).B.(1).1) Low Mg^{2+}-induced impairment of LTP

Low Mg^{2+}-induced impairment of LTP can be explained as follows: NMDA receptor channels relieved from Mg^{2+} block are continuously activated by glutamate in the synaptic cleft, which increases the background level of postsynaptic potential changes (synaptic noise), resulting in an insufficient signal-to-noise ratio for LTP formation. Meanwhile, given that a high concentration of glutamate is released at LTP induction by tetanic electrical stimulation (100 Hz, 1 second), activation of NMDA receptor channels in the resulting state of strong postsynaptic depolarization becomes critical for LTP formation. The inhibitory activity of memantine against NMDA receptor channels shows a membrane potential dependence; inhibition decreases as the membrane potential becomes more positive [see "3.(i).A.(1).1).(c) Activity to block NMDA receptor channels"]. Therefore, the concentration of memantine required to block NMDA receptor channels is considered to increase as the membrane potential becomes more positive. Based on these findings, the results in question can be interpreted as indicating that the impairment of LTP was reduced by memantine at 1 and 10 μmol/L through synaptic noise elimination, but not at 30 μmol/L, at which memantine inhibited even NMDA receptor channel activation necessary for LTP formation.

3.(i).B.(1).2) NMDA-induced learning impairment

NMDA-induced learning impairment can be attributed to interference with LTP resulting from increased synaptic noise due to continuous NMDA receptor channel activation. At 5 and 10 mg/kg, the levels used in the study described in 3.(i).A.(1).2).(b) above, memantine is considered to eliminate synaptic noise interfering with LTP formation for the following reasons: serum memantine concentrations in rats treated at 5 and 10 mg/kg by intraperitoneal injection were 1.0 and 2.3 μmol/L, respectively (Dnaysz W, et al. *Neurosci Biobehav Rev*. 1997;21:455-68); intracerebral (extracellular) and serum memantine concentrations have been reported to be similar to each other (Hesselink MB, et al. *Pharm Res*. 1999;16:637-42); and at 1 μmol/L, memantine reduced impairment of LTP induced by NMDA or low

Mg^{2+} concentration [see Zajaczkowski W et al. *Neuropharmacology*. 1997;36:961-71 and "3.(i).A.(1).2).(a) Effects in model of low magnesium-induced impairment of long-term potentiation"]. However, memantine reduces LTP formation in a concentration-dependent manner (Frankiewicz T, et al. *Br J Pharmacol*. 1996;117:689-97), and is therefore considered to cause learning impairment at higher doses even in an *in vivo* setting. In a study reported in the literature (Misztal M, et al. *Behav Pharmacol*. 1995;6:550-61), the effects of memantine (following intraperitoneal single-agent administration) on passive avoidance learning in normal rats were investigated using the same method as in the study described in 3.(i).A.(1).1).(b) above, and the results showed no effect at 5 mg/kg but learning impairment at 10 and 20 mg/kg. It is therefore assumed that at 10 mg/kg, memantine eliminated NMDA-induced synaptic noise, but caused learning impairment by reducing LTP formation, and consequently failed to reduce NMDA-induced learning impairment.

PMDA asked the applicant to discuss the possibility of whether or not clinical use of memantine at higher doses would induce learning impairment.

The applicant explained as follows:
As activation of NMDA receptors also plays a major role in LTP formation, memantine may induce learning impairment at higher doses by reducing LTP formation in a concentration-dependent manner, even though the drug is a low-affinity NMDA receptor channel antagonist with a rapid but short-lived activity dependent on membrane potential. Meanwhile, the serum memantine concentration in rats at 60 minutes after intraperitoneal administration at 10 mg/kg (the concentration at which the previously mentioned impairment of passive avoidance learning in normal rats has been reported) was shown to be 2.3 μmol/L (412 ng/mL), which was about 2.8-fold the mean serum concentration of 0.83 μmol/L (149 ng/mL) in human subjects after 24 weeks of multiple administration of memantine at 20 mg [see "4.(ii).A.(4).2) Japanese multiple-dose study in patients with AD (b)"]. Therefore, memantine is unlikely to induce learning impairment (a decrease in cognitive function) at or below the clinical maintenance dose of 20 mg.

PMDA considers as follows:
Primary pharmacodynamics studies showed that memantine blocks NMDA channels, and demonstrated its efficacy in several animal models of learning impairment mediated by activation of NMDA receptors. These data indicate the efficacy of memantine in patients with AD. However, given the study results showing that learning impairment was induced at higher doses of memantine, adequate information on learning impairment observed in non-clinical studies should be provided in the package insert. In addition, safety pharmacology studies revealed that memantine potentiated pentetrazol-induced convulsions and produced effects on the central nervous system. Nevertheless, since no central nervous system adverse event of particular concern has been reported in clinical studies [see "4.(iii) Summary of clinical efficacy and safety"], these findings from safety pharmacology studies are unlikely to be of clinical concern.

3.(ii) Summary of pharmacokinetic studies

3.(ii).A Summary of the submitted data

The concentrations of memantine and its metabolites in samples were determined by a validated gas chromatography-mass spectrometry (GC-MS) or liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. Radioactivity in samples was determined by the liquid scintillation counting method. The lower limit of quantitation for plasma memantine concentration was 5 ng/mL in rats, 3 ng/mL in baboons, and 10 ng/mL in rabbits and dogs.

3.(ii).A.(1) Absorption

3.(ii).A.(1).1) Oral administration

(a) Single-dose studies (4.2.2.2.1, 4.2.2.2.2, 4.3.23 [Reference data])

Following a single oral dose of ^{14}C-memantine at 12 mg/kg to male rats (n = 5), radioactivity in blood peaked at 1 hour post-dose and then disappeared in a biphasic manner.

Following a single oral dose of memantine at 25, 50, or 100 mg/kg to male and female rats (male, n = 5 per time point; female, n = 4-5 per time point), the time to maximum plasma concentration (t_{max}) was 0.5 hour (mean) in males and 0.5 to 1.0 hour in females; the maximum plasma concentration (C_{max}) was 1040, 2390, and 4360 ng/mL, respectively, in males and 1640, 2440, and 4940 ng/mL, respectively, in females; and the area under the plasma concentration-time curve from time 0 to infinity after administration (AUC_{∞}) was 6403, 18,424, and 52,158 ng·h/mL, respectively, in males and 9813, 25,492, and 79,681 ng·h/mL, respectively, in females. The elimination half-life ($t_{1/2}$) was 5.74, 7.04, and 6.70 hours, respectively, in males and 5.69, 9.36, and 9.39 hours, respectively, in females.

Following a single oral dose of ^{14}C-memantine at 5 mg/kg to male baboons (n = 2), the peak plasma radioactivity was 1197 ng·eq./mL. The t_{max} was 1.7 hours, and the $t_{1/2}$ was 8 hours.

(b) Repeated-dose studies (4.2.2.2.6, 4.2.3.5.2.2, 4.2.3.2.6, 4.2.3.2.7, 4.2.3.2.10, 4.2.3.7.3.6)

Memantine was administered in the diet for 52 weeks at 20, 40, or 70 mg/kg to male rats (n = 9-10 per time point) and at 15, 30, or 50 mg/kg to female rats (n = 7-10 per time point). In the low-dose group (20 mg/kg for males and 15 mg/kg for females) and the intermediate-dose group (40 mg/kg for males and 30 mg/kg for females), serum memantine concentrations increased in both male and female rats until Week 26, and the concentrations at Week 26 were 2.2- to 3.0-fold those at Week 2 and similar to those at Week 52. In the high-dose group (70 mg/kg for males and 50 mg/kg for females), serum memantine concentrations increased until Week 52, when the concentrations were approximately 4-fold those at Week 2.

Memantine was orally administered to pregnant rabbits (n = 4-5) at 3, 10, or 30 mg/kg for 13 days. The t_{max} and $t_{1/2}$ on Day 1 were 1.0 to 1.2 hours and 2.05 to 3.28 hours, respectively, and the C_{max} and AUC_{∞} increased generally dose-proportionally. The time course of plasma concentrations observed on Day 13 was generally the same as that on Day 1.

Memantine was orally administered to male and female dogs (n = 3 per sex) at sequential, escalating doses of 3, 6, and 9 mg/kg or of 6, 12, and 18 mg/kg, for 5 days at each dose level (for a total of 15 days). The C_{max} and AUC_{∞} on Day 15 at 18 mg/kg were almost 2-fold those at 9 mg/kg. On Day 15, the $t_{1/2}$ was 5.42 to 6.57 hours and the t_{max} was 4.0 hours in females of the 18 mg/kg group and 1.3 to 1.7 hours in other animals. Memantine was orally administered to male and female dogs (n = 6 per sex) in escalating doses for a total of 26 weeks. Treatment was started at a dose of 0.25, 0.75, or 1.5 mg/kg/day, which was titrated weekly to 3, 6, or 12 mg/kg, respectively, at Week 4; to 3, 9, or 15 mg/kg, respectively, at Week 11; and to 3, 9, or 18 mg/kg, respectively, at Week 12. The last dose level was maintained through Week 26. The ratio of plasma memantine concentrations at Week 26 to those at Week 13 (Week 26/Week 13) was approximately 1 (0.84-1.16).

Memantine was orally administered to male and female baboons (n = 2 per sex) at 8 mg/kg for 14 days. The C_{max} and AUC_{∞} of memantine on Day 12, relative to those on Day 1, increased by 2.4- and 2.1-fold, respectively, in males and 1.4- and 1.7-fold, respectively, in females, while the t_{max} and $t_{1/2}$ on Day 12 were similar to those on Day 1. No gender-related differences were observed in the time course of plasma memantine concentrations between Day 1 and Day 12. In male and female baboons (n = 4-6 per sex) that orally received memantine at 2, 4, or 8 mg/kg for 52 weeks, the ratio of plasma memantine concentrations (at 24 hours post-dose) on Week 52 to those on Week 13 (Week 52/Week 13) was <1 (0.73-0.99).

3.(ii).A.(2) Distribution

3.(ii).A.(2).1) Organ and tissue distribution (4.2.2.2.1, 4.2.2.3.1)

Following a single oral dose of ^{14}C-memantine at 80 mg/kg to male albino and pigmented rats (n = 1 per strain per time point), the tissue distribution of radioactivity was evaluated up to 28 days post-dose using whole-body autoradiography. In albino rats, radioactivity levels peaked at 1 or 6 hours post-dose in tissues other than the pancreas, and then declined gradually, falling below the detection limit at 4 days post-dose in all tissues other than the skin. Radioactivity levels were higher in most tissues, except for bones, than in blood, and were particularly high in the gastrointestinal contents, penis, kidney, urinary tract, liver, lung, adrenal gland, lacrimal gland, Harderian gland, salivary gland, and spleen. In pigmented rats, radioactivity levels in the skin were higher in pigment cells than in non-pigment cells at 12 and 24 hours post-dose. Radioactivity was distributed in the basal layer containing melanin cells, and was also detected at a high concentration in the uvea. Radioactivity levels in pigment cells in the skin and uvea peaked at 6 hours post-dose. In albino rats, radioactivity levels in the eyes peaked (7.32 µg·eq./g) at 6 hours post-dose, and then declined rapidly. Meanwhile, in pigmented rats, radioactivity levels in the eye peaked (69.4 µg·eq./g) at 6 hours post-dose, remained higher than those in albino rats, and were still detectable at 28 days post-dose.

Following a single dose of ^{14}C-memantine at 0.5 mg/kg (n = 4-7 per time point) or 12 mg/kg (n = 3 per time point) to male albino rats, radioactivity levels at 24 hours post-dose in the testis, lung, liver, kidney,

and fat in the intestinal tract were 12- to 36-fold those in the blood. Following 5-day once-daily repeated doses of ^{14}C-memantine at 12 mg/kg, tissue radioactivity levels were 2.6-fold those after a single dose, while tissue radioactivity levels were similar between after 10-day repeated doses and after 5-day repeated doses. Elimination of radioactivity after completion of the 10-day repeated doses was slower in the adrenal gland, heart, and thyroid than in other tissues.

3.(ii).A.(2).2) Brain distribution (4.2.2.3.2)

Memantine was administered in the diet to male and female rats (n = 4 per sex per time point) at 30 mg/kg for 29 days. The concentrations of memantine in the brain were measured every 2 hours from 0 to 24 hours after the final dose to calculate the area under the concentration-time curve from 0 to 24 hours (AUC_{0-24}). As a result, the AUC_{0-24} of memantine was higher (18-fold in males and 25-fold in females) in the brain than in plasma.

3.(ii).A.(2).3) Ocular tissue distribution (4.2.3.7.3.1)

When memantine was administered in the diet to male albino and pigmented rats (n = 10 per strain) at 80, 120, or 180 mg/kg for 6 weeks, the concentrations of memantine in plasma and tear fluid on Day 45 were as follows: in albino rats, memantine levels in plasma were 1.7 ± 1.0 (mean ± SD), 3.2 ± 1.1, and 5.8 ± 1.8 μg/mL, respectively, and memantine levels in tear fluid were 24.9 ± 5.8, 36.6 ± 7.9, and 168.0 ± 82.8 μg/g, respectively; and in pigmented rats, memantine levels in plasma were 1.5 ± 0.7, 3.3 ± 1.4, and 8.5 ± 2.1 μg/mL, respectively, and memantine levels in tear fluid were 18.2 ± 6.1, 40.8 ± 22.8, and 114.7 ± 25.2 μg/g, respectively. The concentrations of memantine were high in the Harderian gland (mean; 519.5, 680.5, and 981 μg/g, respectively) in albino rats and in the Harderian gland (380.7, 636.6, and 859.4 μg/g, respectively) and the iris (2304.4 and 6340.1 μg/g after administration in the diet at 80 and 120 mg/kg, respectively) in pigmented rats. The concentrations of memantine in the iris and other ocular tissues in pigmented rats were 37- to 47-fold and 0.73- to 2.9-fold, respectively, those in albino rats.

3.(ii).A.(2).4) Plasma protein binding and distribution in blood cells (4.2.2.3.6, 4.3.24 [reference data])

Plasma samples from male mice, male rats, female rabbits, male dogs, and male and female baboons were spiked with ^{14}C-memantine (final concentration, 100 to 8380 ng·eq./mL in rabbits and 103 to 8360 ng·eq./mL in other animals) and incubated at 37˚C for 15 minutes. The mean proportion of memantine bound to plasma proteins to the total plasma concentration ranged from 33.8% to 45.6% in samples from these animal species, and the protein binding ratio thus showed no species differences or concentration-dependence.

Following 7-day repeated oral doses of ^{14}C-memantine at 5 mg/kg to female baboons (n = 2) once daily (Days 1 and 7) and twice daily (Days 2 through 6), the blood-to-plasma ratio of radioactivity was 0.745.

3.(ii).A.(2).5) Placental-fetal transfer (4.2.2.3.7)

Following a single intravenous dose of ^{14}C-memantine at 10 mg/kg in rabbits on gestation day 19 of (n = 2-3 per time point), radioactivity was detected in the maternal placenta and amniotic fluid and the fetal blood at 0.5 hour post-dose. The radioactivity level in fetal blood was 41% to 54% of that in maternal blood until 4 hours post-dose and similar to that in maternal blood after 24 hours post-dose.

3.(ii).A.(3) Metabolism

3.(ii).A.(3).1) Metabolites in urine (4.2.2.4.4, 4.2.2.4.5, 4.2.2.4.6, 4.2.2.4.7)

Memantine was orally administered to mice at 80 mg/kg once daily in repeated doses for 5 days, to rats at 80 mg/kg in a single dose, and to baboons at 8 mg/kg once daily in repeated doses for 14 days. Urine was collected from mice and rats during the 8 hours after the final dose and from baboons during the 24 hours after the final dose, and was analyzed for memantine metabolites. The following memantine-related substances were detected at a proportion of ≥5% to the total concentration of unchanged and metabolized memantine in urine: unchanged memantine (70.1%) and 3-hydroxymethyl metabolite (10.2%) in mice; 3-hydroxymethyl metabolite (54.2%), unchanged memantine (25.7%), 4-hydroxy metabolite (4-OH, 7.84%), and 3-carboxyl metabolite (6.37%) in rats; and an isomer* of 1-nitro-7-OH (42.4%), 3-hydroxymethyl metabolite (9.99%), 7-OH (9.89%), 6-OH (9.72%), unchanged memantine (8.39%), 4-OH (6.04%), and 1-nitro-7-OH (5.61%) in baboons.

3.(ii).A.(3).2) Induction of hepatic drug-metabolizing enzymes (4.2.2.4.9)

Following 3-day repeated intraperitoneal doses of memantine at 12 mg/kg to male rats (n = 3), the relative content of cytochrome P-450 (CYP) in liver microsomes of the treated animals was similar to that in the saline group. Ethoxyresorufin *O*-dealkylation activity, pentoxyresorufin *O*-dealkylation activity, and aminopyrine *N*-demethylase activity in liver microsomes of rats receiving 3-day repeated intraperitoneal doses of memantine were similar to those in the saline group.

3.(ii).A.(4) Excretion

3.(ii).A.(4).1) Urinary and fecal excretion (4.2.2.2.1, 4.3.23 [reference data], 4.3.24 [reference data], 4.3.26 [reference data])

After a single oral dose of ^{14}C-memantine at 0.5 or 12 mg/kg to male rats (n = 4-7), the radioactivity excreted during the 24 hours post-dose was 78.1% and 79.3%, respectively, in urine and 14.0% and 13.6%, respectively, in feces relative to the administered radioactivity. After a single oral dose of ^{14}C-memantine at 5 mg/kg to male baboons (n = 2), the excreted radioactivity was 58.0% in urine during the 4 days post-dose and 10.3% in feces during the 3 days post-dose relative to the administered radioactivity, and unchanged memantine accounted for 9% of the radioactivity excreted in urine during the 24 hours post-dose.

Male rats (n = 4-7) received ^{14}C-memantine by repeated once-daily oral administration at 0.5 or 12 mg/kg for 10 days. In the 0.5 mg/kg group, the excreted radioactivity was 75.3% in urine from after the

* One of the 3 isomers differing in GC-MS retention time from 1-nitro-7-OH

initial dose to 4 days after the final dose and 21.3% in feces from after the initial dose to 6 days after the final dose relative to the administered radioactivity. In the 12 mg/kg group, the radioactivity excreted from after the initial dose to 6 days after the final dose was 78.5% in urine and 19.8% in feces relative to the administered radioactivity. Male mice (n = 6-7) received ^{14}C-memantine by repeated oral administration at 10 mg/kg three times daily for 3 or 9 days (twice-daily only on Day 9). The radioactivity excreted in urine and feces from after the initial dose to 24 hours after the final dose accounted for 49.7% and 18.9%, respectively, of the administered radioactivity after the 3-day administration and 56.3% and 20.6%, respectively, of the administered radioactivity after the 9-day administration. Female baboons (n = 2) received ^{14}C-memantine by oral administration at 5 mg/kg once daily on Days 1 and 7 and twice daily from Day 2 through Day 6. The radioactivity excreted from after the initial dose to 24 hours after the final dose was 80.7% in urine and 9.4% in feces relative to the administered radioactivity, and unchanged memantine accounted for 7% of the radioactivity in urine.

3.(ii).A.(4).2) Biliary excretion (4.3.26 [reference data])

Following a single intraduodenal dose of ^{14}C-memantine at 10 mg/kg to bile duct-cannulated male mice (n = 5-7), the radioactivity excreted in bile during the 4 hours post-dose was 1.43% of the administered radioactivity. When 10 mg/kg of ^{14}C-memantine was administered orally 3 times daily for 3 days and then intraduodenally by single administration on Day 4, the radioactivity excreted in bile during the 4 hours post-dose on Day 4 was 1.32% of the administered radioactivity.

3.(ii).A.(4).3) Excretion in milk (4.2.2.5.1)

Following a single oral dose of ^{14}C-memantine at 7.22 mg/kg to lactating rats (n = 3), the radioactivity levels from 1 to 48 hours post-dose in milk were approximately 3- to 4-fold those in plasma.

3.(ii).A.(4).4) Excretion in tear fluid (4.2.2.2.6)

Memantine was orally administered to male and female dogs (n = 3 per sex) at sequential, escalating doses of 3, 6, and 9 mg/kg or of 6, 12, and 18 mg/kg, for 5 days at each dose level (for a total of 15 days). Before the final dose, the concentrations of memantine in tear fluid were 3.3- to 4.7-fold those in plasma. At 24 hours after the final dose, the concentrations of memantine in tear fluid were 2.5- to 3.8-fold those in plasma.

3.(ii).B Outline of the review by PMDA

3.(ii).B.(1) Nonlinearity and gender-related differences in plasma and serum memantine concentrations in rats

PMDA asked the applicant to explain why more than dose-proportional increases in AUC_∞ were observed following a single oral dose of memantine in male and female rats, and why AUC_∞ was higher in females than in males.

The applicant explained as follows:

In rats treated with an oral dose of memantine, C_{max} increased generally dose-proportionally in both

males and females, while AUC_{∞} tended to increase more than dose-proportionally. Considering that memantine is metabolized at a higher rate in rats than in other animal species, and is eliminated mainly by metabolism in rats, and given that $t_{1/2}$ showed a trend towards dose-proportional increase, the more than dose-proportional increases in AUC_{∞} were considered attributable to a decrease in clearance due to the limitation of the capacity of drug-metabolizing enzymes. On the other hand, the differences in AUC_{∞} of memantine between female and male rats are considered associated with the gender-related differences of drug-metabolizing enzymes, because the dominance of hydroxylated metabolites in rats can be interpreted as indicating involvement of CYPs in the metabolism of memantine, and the expression of CYP isoforms in rats is known to be sex-specific (Kobliakov V, et al. *Eur J Biochem*. 1991;195:585-91).

PMDA considers as follows:
The evidence is insufficient to support the applicant's explanation that the more than dose-proportional increases in AUC of memantine in rats can be attributable to the higher rate of its metabolism in rats than in other animal species, because the relative composition of metabolites has not been evaluated in the single dose studies in rabbits and repeated dose studies in dogs where dose proportionality could have been examined. However, given that human exposure did not show obvious non-linearity [see "4.(ii) Summary of clinical pharmacological studies"], the more than dose-proportional increases in AUC observed in rats were unlikely to be of clinical concern. Because of the uncertainty about the involvement of CYPs in the metabolism of memantine in rats, the evidence is also insufficient to support that the gender-related differences in rats are attributable to the differences of CYP isoforms between male and female rats. Gender-related differences in humans will be discussed in "4.(ii).B.(6) Effects of gender-related differences in pharmacokinetics of memantine."

3.(ii).B.(2) Gender-related differences in transfer to the brain in rats

Given that in rats, the gender-related difference in the concentration of memantine was larger in the brain than in plasma, PMDA asked the applicant to explain the possibility that there may be gender-related differences in the transfer of memantine to the brain.

The applicant explained as follows:
At the time when the concentration of memantine was measured in male and female rat brains, the female-male ratio (female/male) was 1.8 for both steady state plasma (tissue) concentration (C_{ss}) and $AUC_{0\text{-}24}$. These differences are therefore attributable to gender-related differences in the metabolism of memantine in rats. In the brain, the female-male ratio was 2.4 for both C_{ss} and $AUC_{0\text{-}24}$, and thus the concentration of memantine in the brain was also higher in females than in males. The ratio of brain to plasma memantine concentrations (brain memantine concentration/plasma memantine concentration) was 18 in males and 25 in females, with the female-male ratio (female/male) being 1.39. These results were interpreted as suggesting a gender-related difference in the transfer of memantine to rat brains.

PMDA asked the applicant to discuss the possibility that the gender-related difference in the transfer of

memantine to the brain could translate into any gender-related differences in the effects of memantine on the central nervous system, with reference to the results of toxicity studies.

The applicant explained as follows:
Symptoms possibly related to central nervous system toxicity in rats included abnormal excitement and aggression in the intermediate-dose group (135 mg/kg for males and 120 mg/kg for females) and the high-dose group (200 mg/kg for males and 180 mg/kg for females) in the 13-week repeated dietary administration toxicity study. These symptoms occurred in all rats regardless of sex, with no difference between male and female rats. In the 26-week repeated oral administration toxicity study in dogs at a final dose of 3, 9, or 18 mg/kg, symptoms possibly related to central nervous system toxicity (convulsion, impairment of motor coordination, abnormal gait, and nervous erethism) were observed only in 2 males, which were sacrificed in extremis, in the high-dose group and in no females. In the 52-week repeated oral administration toxicity study in baboons at 2, 4, or 8 mg/kg, no gender-related differences were found in symptoms possibly related to central nervous system toxicity (vomiting, behavioral impairment, and eyelid ptosis). These results were interpreted as ruling out gender-related differences in central nervous system toxicity in animals.

PMDA considers as follows:
Although a gender-related difference was observed in the transfer of memantine to rat brains, given that toxicity studies not only in rats but also in other animal species showed no gender-related differences in symptoms possibly related to central nervous system toxicity, the effects of memantine on the central nervous system is unlikely to differ between males and females. Potential gender-related differences in the transfer of memantine to the brain and effects of memantine on the central nervous system in humans will be further reviewed in "4.(ii).B.(6) Effects of gender-related differences in pharmacokinetics of memantine."

Taking account of the distribution of memantine into tear fluid (at concentrations 3.3- to 4.7-fold in male and female dogs and 12- to 29-fold in male albino and pigmented rats relative to plasma concentrations) observed in non-clinical studies, the ocular toxicity of memantine will be reviewed in "3.(iii).B.(2) Ocular toxicity" and "4.(ii).B.(7) Necessity for a caution about ocular toxicity."

3.(iii) Summary of toxicology studies

3.(iii).A Summary of the submitted data

Toxicity studies conducted on memantine covered single-dose toxicity, repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, mechanism of toxicity, dependence, metabolite toxicity, toxicity of related substances, and juvenile animal toxicity.

3.(iii).A.(1) Single-dose toxicity (4.2.3.1.1, 4.3.33 [reference data])

In single oral dose toxicity studies in ICR mice (n = 8 per sex), SD rats (n = 8 per sex), and mongrel dogs (n = 1 per sex), the approximate lethal dose was determined to be 420 mg/kg in mice, 300 mg/kg

in rats, 50 mg/kg in male dogs, and 75 mg/kg in female dogs. Symptoms after dosing included abnormal gait, tremor, slowed breathing, prone position, and reduced body weight gain in mice and rats, and impairment of motor coordination, ataxia, tremor, convulsion, lateral recumbent position, areflexia, salivation, vomiting, and eye closure in dogs.

3.(iii).A.(2) Repeat-dose toxicity

3.(iii).A.(2).1) Thirteen-week dietary administration toxicity study in rats (4.2.3.2.1, 4.2.3.2.2)

Memantine was administered in the diet for 13 weeks to male and female SD rats (n = 10-20 per sex) at 40, 90, 135, or 200 mg/kg/day (males) and 30, 75, 120, or 180 mg/kg/day (females). Since several rats of both sexes in the maximum-dose group (200 mg/kg/day for males, 180 mg/kg/day for females) died or were sacrificed in extremis during the administration period, the dose of 200 mg/kg/day was reduced to 155 mg/kg/day for males and the dose of180 mg/kg/day to 140 mg/kg/day for females from Week 7 and then reduced to 135 mg/kg/day for males and to 120 mg/kg/day for females from Week 9. No dose was administered from Week 11 onward. Rats that died or were sacrificed in extremis included males in the ≥135 mg/kg/day groups and females in the 180 mg/kg/day group. Events observed in animals treated with memantine at the low dose (40 mg/kg/day for males, 30 mg/kg/day for females) and higher doses included reduced body weight gain and decreased spleen weight in male and female rats, decreased food consumption in males, and prolonged prothrombin time in females. Events observed in animals treated with memantine at the intermediate dose (90 mg/kg/day for males, 75 mg/kg/day for females) and higher doses included hematological changes (e.g., decreased platelet count, increased neutrophil percentage, prolonged prothrombin time), changes in urine characteristics (e.g., low pH, increased urinary casts), and low thymus weight in males and females, genital hypoplasia in males, and decreased food consumption, high adrenal and renal weights, lymphoid hypoplasia, and foamy pulmonary macrophages in females. Events observed in animals treated with memantine at the high dose (135 mg/kg/day for males, 120 mg/kg/day for females) and higher doses included effects on the central nervous system (e.g., abnormal excitement , aggression), biochemical changes in the blood (e.g., high blood urea nitrogen [BUN] and aspartate aminotransferase [AST]), corneal edema, lenticular opacity, lymphoid hypoplasia, atrophy or degeneration of reproductive organs (testis, epididymis, seminal vesicle, and uterus), and foamy pulmonary macrophages in males and females. In the maximum-dose group including rats that died or were sacrificed in extremis, aggression, unkempt hair coat, decreased testicular weight, and testicular atrophy or degeneration were observed. Epididymal hypoplasia did not resolve even after a 4-week recovery period, but corneal edema and lenticular opacity resolved during the 4-week recovery period. Based on the above results, the NOAEL was determined to be <40 mg/kg/day for male rats and <30 mg/kg/day for female rats.

3.(iii).A.(2).2) Twenty six-week repeated oral dose toxicity study in rats (4.2.3.2.3, 4.2.3.2.4)

Memantine was administered in titrated doses to male and female SD rats (n = 24 per sex). Oral administration was started at 0.8, 2.5, or 5 mg/kg/day, which was titrated weekly to 10, 20, or 40 mg/kg/day, respectively, until Week 4; and the dose levels were maintained from Week 4 to Week 26. Reduced body weight gain and increased food consumption in males and females and low spleen weight

in males were observed in the ≥20 mg/kg/day groups and high renal weight in males and low spleen and thyroid gland weights in females were observed in the 40 mg/kg/day group. All of these symptoms resolved during the 4-week recovery period. Since reduced body weight gain and increased food consumption observed in females in the 20 mg/kg/day group were mild in severity, the NOAEL in this study was determined to be 10 mg/kg/day for male rats and 20 mg/kg/day for female rats.

3.(iii).A.(2).3) Fifty two-week dietary administration toxicity study in rats (4.2.3.2.6)

Memantine was administered in the diet for 52 weeks to male and female SD rats (n = 20-30 per sex) at 20, 40, or 70 mg/kg/day (males) and 15, 30, or 50 mg/kg/day (females). Events observed in animals treated with memantine at the low dose (20 mg/kg/day for males, 15 mg/kg/day for females) and higher doses included reduced body weight gain and renal papillary calcification in males and females and decreased food consumption and interstitial nephritis in males. Events observed in animals treated with memantine at the intermediate dose (40 mg/kg/day for males, 30 mg/kg/day for females) and higher doses included increased fluid consumption, changes in urine characteristics (e.g., increased urine output), changes in the kidney (renal papillary congestion, hemorrhage, and pigmentation), increased foamy pulmonary macrophages, and interstitial nephritis in males and females and decreased lymphocyte count and testicular atrophy in males. In the high-dose group (70 mg/kg/day for males, 50 mg/kg/day for females), increased lysosomes in gangliocytes and pigmented epithelial cells in the retina were observed in males and females. All of these findings, except increased fluid consumption and decreased lymphocyte count in males, resolved or subsided during the 6-week recovery period. Based on the above results, the NOAEL was determined to be <20 mg/kg/day for male rats and <15 mg/kg/day for female rats.

3.(iii).A.(2).4) Twenty six-week repeated oral dose toxicity study in dogs (4.2.3.2.7)

Memantine was administered in titrated doses to male and female beagle dogs (n = 6 per sex). Oral administration was started at 0.25, 0.75, or 1.5 mg/kg/day, which was titrated weekly to 3, 6, or 12 mg/kg/day, respectively, and the dose levels were maintained from Week 4. The doses were titrated to 3, 9, or 15 mg/kg/day, respectively, at Week 11, and to 3, 9, or 18 mg/kg/day, respectively, from Week 12 onward. Convulsion, impairment of motor coordination, tachypnea, and other events occurred in 2 male dogs, of which one died and the other was sacrificed in extremis, in the 18 mg/kg/day group, but no memantine-related changes were observed in other animals. No changes were noted after the 4-week recovery period. Based on the above results, the NOAEL was determined to be 9 mg/kg/day.

3.(iii).A.(2).5) Thirteen-week repeated oral dose toxicity study in baboons (4.2.3.2.9)

Memantine was orally administered to male and female baboons (n = 3 per sex) at 2, 4, or 8 mg/kg/day for 13 weeks. Both male and female baboons showed effects on the central nervous system (e.g., behavioral impairment, eyelid ptosis, increased incidence in nervous behaviors) in the ≥2 mg/kg/day groups, tremor of extremities and decreased body weight in the ≥4 mg/kg/day groups, and vomiting in the 8 mg/kg/day group. During the 4-week recovery period, piloerection in males and decreased food consumption and decreased body weight in females were observed in the 8 mg/kg/day group. Based on

the above results, the NOAEL was determined to be <2 mg/kg/day.

3.(iii).A.(2).6) Fifty two-week repeated oral dose toxicity study in baboons (4.2.3.2.10, 4.2.3.2.11, 4.2.3.2.12)

Memantine was orally administered to male and female baboons (n = 4 per sex) at 2, 4, or 8 mg/kg/day for 52 weeks. Both male and female baboons showed effects on the central nervous system (e.g., behavioral impairment, increased incidence of eyelid ptosis) in the ≥2 mg/kg/day groups, decreased body weight in the ≥4 mg/kg/day groups, and vomiting in the 8 mg/kg/day group. No withdrawal syndrome was observed during the 4-week recovery period. Based on the above results, the NOAEL was determined to be <2 mg/kg/day.

3.(iii).A.(3) Genotoxicity

Memantine is considered to have no genotoxic potential since negative results were obtained from bacterial reverse mutation assay (4.2.3.3.1.1), gene mutation test with cultured mammalian cells (4.2.3.3.1.2), *in vitro* chromosomal aberration assay using human peripheral lymphoid cells (4.2.3.3.1.3), and micronucleus assay in mice (4.2.3.3.2.1).

3.(iii).A.(4) Carcinogenicity

3.(iii).A.(4).1) Carcinogenicity study in mice (4.2.3.4.1.4, 4.2.3.4.1.5)

Memantine was administered in the diet to male and female B6C3F1 mice (n = 50 per sex) at 2.5, 10, or 40 mg/kg/day for 113 weeks. The incidence of neoplastic lesions showed no increase attributable to administration of memantine, and the drug was considered to have no carcinogenicity in mice. Reduced body weight gain and dyspnea were observed as nonneoplastic changes.

3.(iii).A.(4).2) Carcinogenicity study in rats (4.2.3.4.1.6, 4.2.3.4.1.7)

Memantine was administered in the diet to male and female SD rats (n = 50 per sex) at 2.5, 10, or 40 mg/kg/day for 129 weeks (males) and 128 weeks (females). Reduced body weight gain was observed in rats receiving memantine at 40 mg/kg/day, and the dose was reduced to 20 mg/kg/day from Week 71 onward. No increases in the incidence of neoplastic lesions associated with the administration of memantine were noted, and the drug was considered to have no carcinogenicity in rats. Nonneoplastic changes observed were reduced body weight gain, dyspnea, calcification of the renal medulla, and increased foamy pulmonary macrophages.

3.(iii).A.(5) Reproductive and developmental toxicity

3.(iii).A.(5).1) Reproductive function and fertility study in rats (4.2.3.5.1.1)

Memantine was orally administered to male and female Wistar rats (n = 24 per sex) at 2, 6, or 18 mg/kg/day, from 60 days prior to mating until 1 day before necropsy for males and from 14 days prior to mating until either gestation day 20 (caesarean section group) or postpartum day 20 (natural parturition group) for females. The following changes were observed in the 18 mg/kg/day group: reduced body weight gain and reduced food consumption in parent animals of both sexes; reduced body

weight gain and delayed ossification of the cervical spine in fetuses; and reduced body weight gain in offspring. Based on the above results, the NOAEL was determined to be 6 mg/kg/day for general toxicity in parent animals, 18 mg/kg/day for reproduction and fertility toxicity in parent animals, and 6 mg/kg/day for toxicity in fetuses and offspring.

3.(iii).A.(5).2) Embryo-fetal development study in rats (4.3.36 [reference data])

Memantine was orally administered to pregnant Wistar rats (n = 22-25) at 2, 6, or 18 mg/kg/day from gestation days 6 to 15. Reduced body weight and reduced food consumption were observed in maternal animals in the ≥6 mg/kg/day groups, and agnathia and renal hypoplasia were observed in fetuses in the 2 mg/kg/day group. These fetal findings were considered to be unrelated to memantine because they were of a spontaneous nature and not dose-related. The effects on body weight and food consumption observed in maternal animals in the 6 mg/kg/day group were mild and not considered toxic. Based on the above results, the NOAEL was determined to be 6 mg/kg/day for maternal general toxicity and 18 mg/kg/day for fetal development.

3.(iii).A.(5).3) Embryo-fetal development study in rabbits (4.2.3.5.2.1, 4.2.3.5.2.2)

Memantine was orally administered to pregnant NZW rabbits (n = 13-15) at 3, 10, or 30 mg/kg/day from gestation day 6 to 18. In maternal animals in the 30 mg/kg/day group, the following changes were observed: staggering, unstable posture, mydriasis, hunched position, lethargy, piloerection, reduced body weight, and reduced food consumption. The following changes were observed in fetuses: hydrocephalus, meningocele, and brain herniation in the 3 mg/kg/day group; meningocele in the 10 mg/kg/day group; and brachyury and abnormal forelimb curvature in the 30 mg/kg/day group. These fetal findings were considered unrelated to memantine because they were of a spontaneous nature and not dose-related, and their incidences did not differ between the memantine groups and the control group. Based on the above results, the NOAEL was determined to be 10 mg/kg/day for maternal general toxicity, and 30 mg/kg/day for fetal development.

3.(iii).A.(5).4) Effects on pre- and postnatal development, including maternal function, in rats (4.2.3.5.3.1)

Memantine was orally administered to pregnant Wistar rats (n = 22-25) at 2, 6, or 18 mg/kg/day from gestation day 15 to postpartum day 20. In the 18 mg/kg/day group, reduced body weight, reduced body weight gain, and reduced food consumption were observed in maternal animals and reduced body weight gain was observed in the offspring. Based on the above results, the NOAEL for maternal animals and the offspring was determined to be 6 mg/kg/day.

3.(iii).A.(6) Other toxicity studies

3.(iii).A.(6).1) Studies on the mechanism of toxicity

Since ocular lesions were observed in a 13-week toxicity study by dietary administration in rats and memantine has an affinity for melanin, an ocular toxicity study by dietary administration was conducted in albino and pigmented rats to compare the effects of memantine on ocular tissues with or without

melanin. Neuronal cell toxicity was also evaluated because memantine is a non-competitive NMDA receptor antagonist, and NMDA receptor antagonists have been reported to cause neuronal vacuolization (Olney's lesion) in the rat splenium corporis callosi and cingulate cortex (Olney JW, et al., *Science*. 1989;244:1360-2, Olney JW, et al., *Science*. 1991;254:1515-8).

(a) Ocular toxicity study (4.2.3.7.3.1, 4.2.3.7.3.2)

Memantine was administered in the diet to male albino and pigmented rats (n = 10) at 80, 120, or 180 mg/kg/day for 6 weeks. Corneal lesions (e.g., malformation, keratitis), localized lenticular opacities, and retinal pigment epithelial hypertrophy were observed in both strains of rats. Corneal lesions occurred frequently in pigmented rats while lenticular lesions occurred frequently in albino rats. Memantine was detected in the uvea and Harderian gland at a high concentration [see "3.(ii).A.(2).3) Ocular tissue distribution"], but no histological changes were observed. Therefore, the property of memantine to accumulate in melanin-containing tissues is unlikely to be related to the development of eye lesions. Meanwhile, histological changes in the cornea were observed only on the epithelial side. In addition, the memantine concentration in tear fluid was approximately 10- to 30-fold that in the plasma [see "3.(ii).A.(2).3) Ocular tissue distribution"]. These findings suggest that the corneal lesions may have been attributed to a high concentration of memantine in tear fluid.

Memantine was administered in the diet to male albino and pigmented rats (n = 10-14) at 120 or 160 mg/kg/day for 6 weeks, which was followed by a 4-week recovery period. Although mild ocular opacity was observed in both strains of rats after the 6-week administration, this was a very minor change with no histological abnormalities, and resolved during the recovery period. Systemic changes observed in both strains of rats also resolved during the recovery period. Only pigmented rats exhibited self-biting (bite), which was likely to be a withdrawal symptom, during the recovery period.

(b) Neurotoxicity study (4.2.3.7.3.3, 4.2.3.7.3.4, 4.2.3.7.3.5, 4.2.3.7.3.6)

Memantine was administered to male and female SD rats (n = 2-4 per sex) at a single oral gavage dose of 25, 50, or 100 mg/kg/day, at repeated oral gavage doses of 12.5, 25, or 50 mg/kg/day for 14 days, or at repeated dietary doses of 25, 50, or 100 mg/kg/day for 14 days, and the tissue samples of their splenium corporis callosi and cingulate cortices were examined. As a result, although neuronal necrosis or vacuolization was observed, no neuronal effects were observed at a single oral gavage dose of ≤50 mg/kg/day, at repeated oral gavage doses of 12.5 mg/kg/day in females and ≤25 mg/kg/day in males, and at repeated dietary doses of ≤50 mg/kg/day. The serum concentration of memantine following repeated dietary doses of 50 mg/kg/day, at which no neuronal effects were observed, was estimated to be approximately 550 ng/mL.

Following continuous intravenous infusion of memantine in female SD rats (n = 2-7) for 6 hours (at 7.82 or 15.65 mg/kg/h) or 18 hours (at 3.14 or 6.28 mg/kg/h), the tissue samples of their splenium corporis callosi and cingulate cortices were examined. Regardless of the dose or schedule, the incidence of neuronal necrosis or vacuolization was higher in the memantine groups than in the control group

(normal saline).

Following 14-day repeated oral doses of memantine at 8 mg/kg/day to male and female baboons (n = 2 per sex), no neuronal vacuolization or necrosis was observed in the cingulate cortex. The C_{max} on Day 12 was 397 ng/mL.

3.(iii).A.(6).2) Dependence studies

Since withdrawal syndrome was observed in pigmented rats during the recovery period of the ocular toxicity studies in albino and pigmented rats, follow-up studies were conducted to examine whether or not discontinuation would induce withdrawal syndrome.

(a) Dietary administration toxicity study in albino and pigmented rats for six weeks followed by a four-week recovery test (4.2.3.7.4.1)

Memantine was administered in the diet to male albino and pigmented rats (n = 12-16) at 40, 80, or 160 mg/kg for 6 weeks, which was followed by a 4-week recovery period. In the 40 and 80 mg/kg/day groups, reduced body weight and reduced food consumption were observed in both strains during the first week of the recovery period. Self-biting behavior (injury of the front limb, hind limb, scrotum, or tail) was observed in 7 of the 13 pigmented rats in the 160 mg/kg/day group but in none of the albino rats. Self-biting behavior disappeared in 5 of the 7 rats after administration of memantine was resumed at 160 mg/kg/day. These results were interpreted as suggesting that all abnormalities (reduced body weight, reduced food consumption, and self-biting behavior) observed during the recovery period were signs of withdrawal syndrome, and that memantine may cause physical dependence in rats when administered in the diet for 6 weeks.

(b) Continuous intravenous self-administration study in rhesus monkeys (4.2.3.7.4.2)

Male and female rhesus monkeys (n = 2 per sex) were allowed to self-administer memantine at sequential doses of 0.06, 1.25, and 0.25 mg/kg/dose, for 2 weeks at each dose level, and subsequently received intravenous memantine at 1 mg/kg every 6 hours (forced administration) for 28 days. The frequency of self-administration did not exceed the predefined criterion (10 times per day) in any animals, which was interpreted as indicating the absence of a reinforcement effect. During a 3-day recovery period following the forced administration period, 1 of the 4 animals exhibited withdrawal syndrome manifesting as reduced food consumption, muscle stiffness, and increased aggression toward the observer. Since the highest plasma concentration of memantine measured during the forced administration period was 646 ng/mL among the other 3 animals that showed no withdrawal syndrome, physical dependence was considered unlikely to occur when the plasma concentration is ≤650 ng/mL.

3.(iii).A.(6).3) Metabolite toxicity studies

The safety of the N-gludantan conjugate (conjugation via the amino group to glucuronide in the furanose form), a major human metabolite of memantine, was evaluated in a single-dose toxicity study in rats and genotoxicity studies (bacterial reverse mutation assay and *in vitro* chromosomal aberration assay

using human peripheral blood lymphocytes). The safety of repeated administration of the N-gludantan conjugate was deemed to have already been evaluated because the exposure to this metabolite was lower in humans (AUC of 173 ng·h/mL at 20 mg/day) than in rats in the high-dose group (AUC of 406-561 ng·h/mL) in a 13-week dietary administration toxicity study.

(a) Single-dose toxicity study in rats (4.2.3.7.5.1)

A single dose of the N-gludantan conjugate was administered intravenously at 40 mg/kg or intraperitoneally at 70, 140, or 280 mg/kg to female SD rats (n = 5) while a single intravenous dose of memantine was administered to the control group at 30, 36, or 43 mg/kg. In the groups treated with the N-gludantan conjugate, no animals died, and only mild changes (decreased activity, ataxia, dyspnea, and hypotonia) were observed. Therefore, a single-dose of the N-gludantan conjugate was considered to have lower toxicity than memantine.

(b) Genotoxicity studies (4.2.3.7.5.2, 4.2.3.7.5.3)

In a bacterial reverse mutation assay, the N-gludantan conjugate did not increase the number of revertant colonies. In an *in vitro* chromosomal aberration assay in human peripheral blood lymphocytes, a significant increase was observed in the frequency of chromosomal aberrations in a 24-hour treatment (5000 μg/mL) without metabolic activation. The increased frequency of chromosomal aberrations was considered attributable to hyperosmolarity and the duration of exposure to the conjugate. The above results suggested that the N-gludantan conjugate has no genotoxicity.

3.(iii).A.(6).4) Toxicity studies on related substances

The safety of related substances (related substances A and B) in the formulation was evaluated in a 13-week dietary administration toxicity study in rats using forcefully degraded samples of the drug product. In addition, a bacterial reverse mutation assay and an *in vitro* chromosomal aberration assay using cultured cells were performed using synthesized related substances A and B.

(a) Thirteen-week dietary administration toxicity study in rats (4.2.3.7.6.1)

Male and female SD rats (n = 10 per sex) received the drug product, either a non-degraded formulation at 120 mg/kg/day (as memantine) or a forcefully degraded formulation at 30 or 120 mg/kg/day (as memantine), for 13 weeks in the diet. The findings were similar between the non-degraded formulation 120 mg/kg/day group and the forcefully degraded formulation 120 mg/kg/day group, and this result was interpreted as showing the absence of specific toxicity due to related substances. The amounts of related substances A and B contained in a dose of 120 mg/kg/day of the forcefully degraded formulation were 5 and 1.7 mg/kg/day, respectively.

(b) Genotoxicity studies (4.2.3.7.6.2, 4.2.3.7.6.3)

Based on the negative results of the bacterial reverse mutation assay and the *in vitro* chromosomal aberration assay, the related substances (Related Substances A and B) are considered to have no genotoxicity.

3.(iii).A.(6).5) Juvenile rat study (4.3.43 [reference data])

Male and female SD rats (aged 14 days; n = 32 per sex) received memantine at 15, 30, or 45 mg/kg/day by single administration or repeated oral administration for 3 or 57 days. No deaths occurred. Findings in the ≥30 mg/kg/day groups included delayed preputial separation in males, delayed vaginal opening in females, and reduced body weight gain in both sexes. Findings in the 45 mg/kg/day group included reduced food consumption (for 2 weeks after weaning), increased degeneration of the nucleus ventralis anterior thalami (1 and 3 days after the single dose), and increased degeneration of the nucleus mamillaris lateralis (1 day after the single dose) in both sexes and decreased habituation to auditory stimuli in males. The delayed preputial separation and delayed vaginal opening had no effects on the reproductive function. Based on the above results, the NOAEL was determined to be 15 mg/kg/day.

3.(iii).B Outline of the review by PMDA

3.(iii).B.(1) Neurotoxicity

PMDA asked the applicant to explain the mechanism of the development of neuronal vacuolization in the cingulate cortex observed in the rat neurotoxicity studies in which a single oral dose and repeated oral doses of memantine were administered.

The applicant explained as follows:

Cingulate cortex neurons have muscarinic receptors, i.e., ACh receptors, and the release of ACh in the vicinity of these receptors is regulated by GABA neurons. Meanwhile, NMDA receptors are located on GABA neurons, and inhibition of NMDA receptors on GABA neurons by an NMDA receptor channel antagonist eliminates GABA-mediated regulation of ACh release. Therefore, inhibition of NMDA receptors on GABA neurons by memantine is considered to induce continuous ACh release resulting in histological damage to cingulate cortical neurons due to excess ACh (Olney JW, et al. *Science*. 1991;254:1515-8).

In the 14-day dietary administration study in rats, no neurotoxicity was observed in either sex in the 50 mg/kg/day group. The C_{ss} and AUC of memantine in female rats, which were found to have higher exposure in the study, were estimated to be 565 ng/mL and 13,560 ng·h/mL, respectively, while the estimates for these parameters at the clinical dose level (20 mg/day) were 149 ng/mL and 3576 ng·h/mL, respectively. These values provide an approximately 3.8-fold safety margin in terms of neurotoxicity. In the 52-week dietary administration toxicity study in rats, no neuronal effects were observed in the high-dose group (70 mg/kg/day) despite a serum memantine concentration of 3248 ng/mL in this group at the end of the treatment period. This may suggest that the neuronal effects of memantine are affected not only by its serum concentrations but also by the patterns of concentration changes, and a gradual increase in blood concentration may become unlikely to produce neuronal effects. As described above, the safety margin is approximately 3.8 times the clinical dose and the neurotoxic effects is unlikely to appear when blood memantine concentrations increase gradually. In addition, the increase in blood memantine concentrations will also be gradual in clinical use. Therefore, memantine is unlikely to cause

neurotoxicity in the clinical setting.

3.(iii).B.(2) Ocular toxicity

PMDA asked the applicant to explain the safety of memantine in humans in consideration of the corneal and lenticular findings in repeat-dose toxicity studies in rats.

The applicant stated that corneal anomalies were considered attributable to local circulatory disturbance as well as high local exposure to memantine (in the cornea and tear fluid), and that the mechanisms underlying lenticular opacity have not been elucidated, and then provided the following explanations about the safety of memantine in humans. Considering that the concentration of memantine in human tear fluid after administration of memantine at 20 mg/day was approximately 395 ng/mL [see "4.(ii).A.(4).3) Excretion in tear fluid during multiple doses"], and that the concentrations of memantine in tear fluid in rats and dogs without corneal lesions were approximately 25 and 1.1 μg/mL, respectively [see "3.(ii).A.(2).3) Ocular tissue distribution," and "3.(ii).A.(4).4) Excretion in tear fluid"], the safety margin for corneal malformation in humans is 63-fold that in rats and 2-fold that in dogs, respectively. On the assumption that the concentration of unchanged memantine in the human cornea is 2-fold (approximately 790 ng/g) that in tear fluid, as shown in rats, the safety margin is estimated to be approximately 8-fold the concentration of memantine in the rat cornea without lesions (6.6 μg/g). Furthermore, a comparison of the AUC in rats without corneal lesions (approximately 36,000 ng·h/mL) with the AUC at the clinical dose level (3576 ng·h/mL) provides an approximately 10-fold safety margin. Therefore, administration of memantine to humans is unlikely to cause corneal lesions. In Japanese placebo-controlled, double-blind, comparative studies, the incidence of ocular adverse events was similar between the memantine groups and the placebo group, with no particular issues of concern. Localized lenticular opacity would not be a serious toxic change because of its localized nature and the absence of obvious histological abnormalities in lens fibers. In the 6-week dietary administration toxicity study in albino and pigmented rats, no lenticular abnormalities were found at dose levels up to 120 mg/kg/day, at which the AUC was approximately 76,800 ng·h/mL, and its comparison with the AUC at the clinical dose in humans (3576 ng·h/mL) provides an approximately 21-fold safety margin. Lenticular abnormalities were monitored with a slit-lamp microscope during a clinical pharmacology study (Study IE2201), phase III studies (Studies IE3501 and MA3301), and a long-term study (Study MA3302) conducted in Japan, all of which identified no issues of clinical concern except for 1 case (0.1%) of lenticular opacity reported in the memantine group (10 or 20 mg group). The above results demonstrated that memantine is unlikely to cause lenticular lesions in humans.

3.(iii).B.(3) Physical dependence

PMDA asked the applicant to provide explanations for the effects on the central nervous system including withdrawal syndrome observed specifically in pigmented rats in the 6-week dietary administration comparative toxicity study and 4-week recovery test in albino and pigmented rats.

The applicant explained as follows:

Although it is unclear why the effects of memantine on the central nervous system were observed specifically in pigmented rats, the effects may be attributed to the strain-dependent differences; there is a possibility that a larger amount of dopamine may have been released by dopaminergic neurons in the basal ganglia in pigmented rats exposed to a higher concentration of memantine than in albino rats, resulting in drug dependence with apparent withdrawal syndrome noted in pigmented rats. This interpretation is built on the following findings: (a) memantine has an affinity for melanin; (b) a large number of neuromelanin-containing neurons are present in the basal ganglia of pigmented rats; (c) many neurons in the basal ganglia are dopaminergic (Dahlstroem A and Fuxe K. *Acta Physiol Scand*. 1964;232[suppl]:1-55); and (d) memantine promotes dopamine release (Spanagel R, et al. *Eur J Pharmacol*. 1996;296:239-46). Moreover, activation of dopaminergic neurons and the consequent enhancement of motor and other functions may have contributed to increased activities and the high incidence of aggression. Withdrawal syndrome was also observed in 1 of the 4 rhesus monkeys in the continuous intravenous self-administration study. Taking into account that the plasma concentration of memantine was 131 to 646 ng/mL in the other 3 rhesus monkeys without withdrawal syndrome, physical dependence is unlikely to occur at a plasma memantine concentration of ≤650 ng/mL. Given that the plasma concentration is 149 ng/mL when memantine is administered at the usual clinical dose in humans (20 mg/day), there is no conceivable clinical concern.

3.(iii).B.(4) Nephrotoxicity

The applicant provided the following explanations for the interstitial nephritis, renal papillary calcification, renal papillary hemorrhage and congestion, and increased calcification of the renal medulla observed in the repeat-dose toxicity study and the carcinogenicity study in rats:

These findings were considered to represent the early changes associated with chronic progressive nephropathy (CPN), an aging-associated disease, the onset of which is delayed by dietary restriction (Keenan KP, et al. *Toxicol Pathol*. 2000;28:788-98). Therefore, reduced food consumption due to memantine dosing is considered to have delayed the onset of CPN, with its early changes developing at the end of the 52-week dietary administration toxicity study. In the rat carcinogenicity study, the increased calcification of the renal medulla was observed not only in the high-dose group but also in the control group, and was therefore an aging-associated change. The increase in the incidence of calcification was considered to be due to cell damage resulting from urine acidification associated with memantine administration.

In response to the applicant's explanation above ("cell damage resulting from urine acidification"), PMDA asked the applicant to discuss the safety of memantine by comparing its urinary concentrations in rats at doses at which increased calcification of the renal medulla was observed and those in humans at the clinical dose.

The applicant explained that this event did not suggest serious nephrotoxicity for the following reasons: (a) a comparison of the urinary concentration of memantine in rats without increased calcification of the renal medulla (41,200 ng/mL) at the dose level of 10 mg/kg/day in the rat carcinogenicity study and the

urinary concentration in humans at 20 mg/day (11,214 ng/mL) provided a 3.7-fold safety margin; (b) calcification of the renal medulla is unlikely to occur in humans because decreased urine pH has not been reported as adverse events in clinical studies; and (c) all the findings reported in the rat toxicity study were minor changes without fluctuations in biochemical parameters indicative of renal impairment, and showed reversibility when dosing was discontinued.

Although the applicant's responses described in Sections 3.(iii).B.(1) through 3.(iii).B.(4) are generally understandable, PMDA considers that an appropriate caution statement should be included in the package insert in terms of neurotoxicity.

4. Clinical data

4.(i) Summary of biopharmaceutic studies and associated analytical methods

4.(i).A Summary of the submitted data

The concentrations of memantine and its metabolites in samples in studies submitted as the evaluation data were determined using validated GC-MS or LC-MS/MS. The lower limit of quantitation for memantine was 0.5 ng/mL (4 ng/mL in Study 11653A only) in plasma, 5 ng/mL (86 ng/mL in Study MRZ90001-9601 and 20 ng/mL in Study MEM-PK-15) in urine, 5 ng/mL in tear fluid, and 0.5 ng/mL in spinal fluid. The lower limit of quantification for the N-gludantan conjugate (conjugation via the amino group to glucuronide in the furanose form) was 0.879 ng/mL in plasma and spinal fluid and 8.8 ng/mL in urine and that for the 4-OH metabolite and the 6-OH metabolite was 1 ng/mL in plasma, urine, and spinal fluid.

4.(i).A.(1) Bioequivalence

The formulation used in the Japanese late phase II study (Study IE2101 [double-blind phase]) and subsequent studies was identical to the proposed commercial formulation. A bioequivalence (BE) study was conducted in Japanese healthy adult male subjects to prove the BE between the 5, 10, and 20 mg tablets of the proposed commercial formulation.

4.(i).A.(1).1) BE study between 5 and 10 mg tablets (5.3.1.2.1, Study IE1301)

An open-label, 2-treatment, 2-period crossover study was conducted in 18 Japanese healthy adult male subjects to evaluate the BE between the 5 and 10 mg tablets of the proposed commercial formulation (with a washout period of 21 days). The geometric mean ratios of the C_{max} and the area under the plasma concentration-time curve from time 0 to the last time point ($AUC_{0\text{-last}}$) after a single oral dose of two 10 mg tablets versus four 5 mg tablets of the proposed commercial formulation were 0.8918 (90% confidence interval [CI], 0.8536-0.9317) and 0.9714 (0.9477-0.9957), respectively, which were within the predefined BE range (0.80-1.25).

4.(i).A.(1).2) BE study between 10 and 20 mg tablets (5.3.1.2.2, Study IE1602)

An open-label, 2-treatment, 2-period crossover study was conducted in 18 Japanese healthy adult male subjects to evaluate the BE between the 10 and 20 mg tablets of the proposed commercial formulation

(with a washout period of 21 days). The geometric mean ratios of the C_{max} and the $AUC_{0\text{-last}}$ after a single oral dose of one 20 mg tablet versus two 10 mg tablets of the proposed commercial formulation were 1.0471 (1.0175-1.0776) and 1.0335 (0.9943-1.0741), respectively, which were within the predefined BE range.

4.(i).A.(1).3) Dissolution behaviors of formulations (3.2.P.2.2)

Dissolution behaviors of the formulations used in foreign clinical studies (formulations manufactured by Merz and by Forest Pharmaceuticals Inc. [Forest]), a Japanese phase I study (Study IE1801), and an early phase II study (Study IE2901), and of the proposed commercial formulation were evaluated by the paddle method under the following conditions: 50 rpm, 37˚C, test solution volume of 900 mL, 12 vessels, 4 different test solutions (pH 1.2, pH 4.0, pH 6.8, and water), and test solution collection time of [redacted] minutes. The mean dissolution rate in [redacted] minutes was ≥[redacted]% for all formulations in all conditions.

4.(i).A.(2) Food effect study in foreign subjects (5.3.3.4.1, Study MEM-PK-01)

The effect of food on the pharmacokinetics of a single dose of memantine at 20 mg (two 10 mg tablets) was evaluated in a crossover fashion in 23 foreign healthy adult subjects (with a washout period of ≥21 days). The pharmacokinetic parameters after administration of a single oral dose of memantine at 20 mg in the fasted and fed states are as follows: the median t_{max} was 5.6 and 5.0 hours, respectively; the C_{max} was 24.4 ± 4.4 (mean ± SD) and 24.7 ± 4.4 ng/mL, respectively; the AUC_{∞} was 1939.7 ± 472.1 and 1898.9 ± 444.3 ng·h/mL, respectively; and the mean $t_{1/2}$ was 55.6 and 55.9 hours, respectively. The 90% confidence intervals for the geometric mean fed-to-fasted ratios of the C_{max} and AUC_{∞} were 0.98 to 1.05 and 0.95 to 1.02, respectively.

4.(i).A.(3) Mass balance study (5.3.3.1.3, Study HUK610/13 [reference data])

Six foreign healthy adult male volunteers received multiple oral doses of memantine at 5 mg 3 times daily for 19 days, including a single oral dose of ^{14}C-memantine at 5 mg as the first dose on Day 13. The cumulative excretion of radioactivity in urine up to 20 days after administration of ^{14}C-memantine was 83.16% of the dose and that in feces up to 7 days after administration of ^{14}C-memantine was 0.539% of the dose. Based on these data, absorption of memantine by the oral route was estimated to be ≥80% of the dose.

The major urinary metabolites were the N-gludantan conjugate, the 6-OH metabolite, and the 4-OH metabolite. The percentages of these metabolites to the total radioactivity concentration in the urine samples collected over a period from 0 to 24 hours after the final dose were 68.7% for unchanged memantine, 12.9% for the N-gludantan conjugate, 6.51% for the 6-OH metabolite, and 5.87% for the 4-OH metabolite.

4.(i).A.(4) Absolute bioavailability study (5.3.1.1.1, Study HUK610/4 [reference data])

A 4-period crossover study was conducted in 12 foreign healthy adult male subjects to evaluate the absolute bioavailability (BA) by administering single oral doses of 10, 20, and 40 mg of memantine and

a single intravenous dose of 20 mg of memantine (with a washout period of 21 days). The C_{max} and AUC_{∞} were 47.98 ng/mL and 4269 ng·h/mL, respectively, after the single oral dose of 40 mg and 28.70 ng/mL and 2220 ng·h/mL, respectively, after the single intravenous dose of 20 mg. The absolute BA of the single oral dose of 40 mg of memantine was calculated to be 97.0%.*

While the absolute BA of the single oral dose of 10 and 20 mg was calculated to be 148.9% and 120.4%, respectively, these values were considered as reference data because the plasma concentration of memantine was around the lower limit of quantitation (5 ng/mL) at each time point after the oral dose of 10 mg and at the final time point during the elimination phase after other doses, and because the AUC_{∞} after the oral doses of 10 and 20 mg could not be calculated for some of the subjects.

4.(i).B Outline of the review by PMDA

The applicant submitted in this application the results of a food-effect study in foreign healthy subjects (Study MEM-PK-01) using a formulation manufactured by Forest (the formulation used for the development of memantine in the US). Forest's formulation is different from the formulation proposed for marketing in Japan. The applicant explained the reason why a food-effect evaluation had not been conducted in Japanese subjects using the to-be-marketed formulation.

(a) The measured plasma concentrations of memantine in patients with AD after repeated doses in the fed state generally agreed with the values simulated from plasma memantine concentrations in elderly individuals after a single dose in the fasted state. Therefore, the BA of memantine was considered unlikely to be affected by food.
(b) A dissolution test of the drug product showed that the mean dissolution rate in [redacted] minutes was ≥[redacted]% in any of the test solutions (first fluid for disintegration test specified in the Japanese Pharmacopoeia, pH 1.2; diluted McIlvaine buffer solution, pH 4.0; second fluid for disintegration test specified in the Japanese Pharmacopoeia, pH 6.8; and water), indicating fast dissolution. Therefore, postprandial changes in gastric pH were considered unlikely to affect gastrointestinal absorption of memantine.
(c) Absorption of memantine was considered unlikely to fluctuate because its absolute BA is as high as 97.0%. Since memantine is a renally excreted drug, the metabolism and biliary excretion of memantine are also unlikely to fluctuate with postprandial increases in hepatic blood flow and bile secretion, and other factors
(d) No food effect was observed in Study MEM-PK-01 in which the effects of food on the BA of memantine were evaluated in foreign healthy adult subjects after administration of 10-mg tablets manufactured by Forest.

Based on the above reasoning, the pharmacokinetics of memantine is unlikely to be affected by food. Therefore, no clinical study was conducted to evaluate the effects of food using the to-be-marketed formulation in Japan.

* A value calculated with correction based on a dosage considering the content of memantine in the formulation.

PMDA considers as follows:

The level of formulation changes between the to-be-marketed 10-mg tablets and the Forest 10-mg tablets used in Study MEM-PK-01 is "E" according to the "Guideline for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms" (PFSB/ELD Notification No. 1124004 dated November 24, 2006; hereinafter referred to as the Formulation Change BE Guideline). Therefore, it cannot be considered that the effects of food on the BA of memantine were evaluated using a formulation proven to be bioequivalent to the to-be-marketed 10-mg tablets. However, the high absolute BA shown for memantine is unlikely to be affected significantly by differences in formulation. Both Forest formulation and the to-be-marketed formulation showed rapid dissolution independent of the pH of the test solution, indicating similarity in dissolution behavior. The effects of food are expected to be small based on the results of the comparison between the plasma memantine concentrations measured in patients with AD after multiple doses in the fed state and those simulated from the plasma memantine concentrations in elderly individuals after a single dose in the fasted state. Therefore, PMDA concluded that the absence of clinical studies evaluating the effects of food on the BA using the to-be-marketed formulation, except for Study MEM-PK-01, is unlikely to be of major clinical concern.

4.(ii) Summary of clinical pharmacology studies

4.(ii).A Summary of the submitted data

4.(ii).A.(1) *In vitro* studies using human biomaterials

4.(ii).A.(1).1) Plasma protein binding (5.3.2.1.1, 5.3.3.1.3)

In human plasma spiked with ^{14}C-memantine (0.5-10 μmol/L [final concentration]), the protein binding ratio of memantine was 41.9% to 45.3%.

A 4.5% human serum albumin solution, a 0.09% human α_1-acidic glycoprotein (α_1-AGP) solution, and a 1.0% human gamma-globulin solution were spiked with ^{14}C-memantine (103 ng/mL [final concentration]) and incubated at 37˚C for 15 minutes. The protein binding ratio of memantine was 20.5% in the human serum albumin solution, 10.7% in the human α_1-AGP solution, and 3.3% in the human gamma-globulin solution.

4.(ii).A.(1).2) *In vitro* metabolism in human liver

(a) Metabolism of memantine (5.3.2.2.1)

Immortalized human liver epithelial cells expressing human CYP enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4) were incubated in culture media containing memantine (10 or 100 μmol/L) at 37˚C for 2 or 24 hours. The percent reduction in the concentration of memantine in the culture media after incubation for 2 and 24 hours was 20.7% and 21.9%, respectively, for cells expressing no human CYP enzymes and 15.0% to 22.1% and 13.4% to 28.0%, respectively, for CYP-expressing cells.

(b) Enzyme inhibition (5.3.2.2.5)

Using human liver microsomes, memantine (0.1, 1, or 10 μmol/L [final concentration]) was evaluated for its inhibitory effects on CYP enzymes (CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP2E1, CYP3A4), flavin-containing monooxygenase (FMO), epoxide hydrolase (EH), UDP-glucuronosyltransferase (UGT), and sulfotransferase (SULT). Inhibitory effects on CYP enzymes, FMO, and EH were also examined after preincubation with memantine. Irrespective of preincubation, memantine did not inhibit the activity of any CYP enzyme, EH, UGT, or SULT. Meanwhile, the activity of FMO was inhibited by approximately 40% only when preincubated with memantine (10 μmol/L) compared to the activity when preincubated without memantine.

(c) Enzyme induction (5.3.2.2.4)

The activities of CYP1A2, CYP2C9, CYP2E1, and CYP3A4/5 in human liver cells incubated for 3 days in culture media containing memantine (0.1, 1,0, or 10 μmol/L) were similar to those of negative controls (0.1% DMSO and 0.1% saline).

4.(ii).A.(2) Studies in healthy adult subjects

4.(ii).A.(2).1) Single-dose studies

(a) Japanese single-dose study (5.3.3.1.1, Study IE1801)

In 24 Japanese healthy adult male subjects who received a single oral dose of memantine at 5, 10, 20, or 40 mg in the fasted state, the mean t_{max} was 5.3, 5.3, 6.0, and 4.5 hours, respectively; the C_{max} was 6.86 ± 0.66 (mean ± SD), 12.18 ± 1.68, 28.98 ± 3.65, and 60.11 ± 13.08 ng/mL, respectively; and the AUC_{∞} was 489.4 ± 51.0, 1091.7 ± 172.7, 2497.6 ± 482.8, and 4794.0 ± 572.3 ng·h/mL, respectively, all showing a generally dose-proportional increase. The mean $t_{1/2}$ was 55.3, 63.1, 71.3, and 57.3 hours, respectively.

The concentration of memantine in tear fluid was 12.70 ± 3.85 (mean ± SD), 24.88 ± 6.08, 43.44 ± 17.13, and 128.53 ± 35.37 ng/mL, respectively, at 4 hours post-dose and 9.20 ± 2.75, 16.84 ± 3.56, 34.58 ± 13.47, and 85.46 ± 18.57 ng/mL, respectively, at 52 hours post-dose, showing almost dose-proportional increases. The ratio of tear fluid to plasma concentrations at each dose level ranged from 1.68 to 2.47 at 4 hours post-dose and from 2.32 to 2.78 at 52 hours post-dose.

The cumulative urinary excretion was 34.84% to 43.39% during the first 72 hours after administration at all dose levels and 59.21% during the first 168 hours after administration at 20 mg.

4.(ii).A.(2).2) Multiple-dose studies

(a) Foreign multiple-dose study (5.3.3.1.2, Study MRZ90001-9704 [reference data])

Pharmacokinetics of memantine (immediate-release and extended-release tablets) was investigated in 48 foreign healthy adult subjects who received multiple doses at 10 mg for the first 5 days and then at 20 mg for the subsequent 20 days. The pharmacokinetic study results for the immediate-release tablets in 18 male and 6 female subjects are as follows: The trough plasma concentration of memantine was

65.66 ± 16.17 ng/mL (mean ± SD) on Day 18 and 62.51 ± 18.37 ng/mL on Day 25. The maximum steady state plasma concentration ($C_{max, ss}$) after the final dose was 85.83 ± 22.87 ng/mL (76.7 ±15.7 ng/mL in male subjects and 113.1 ± 19.3 ng/mL in female subjects) and the area under the plasma concentration-time curve from time 0 to 24 hours after administration at steady state ($AUC_{24, ss}$) was 1803 ± 492 ng·h/mL (1620 ± 373 ng·h/mL in male subjects and 2352 ± 397 ng·h/mL in female subjects).

4.(ii).A.(3) Study in elderly subjects

4.(ii).A.(3).1) Single-dose study in healthy elderly Japanese and Caucasian subjects (5.3.3.3.4, Study IE1302)

A total of 24 healthy elderly Japanese and Caucasian male subjects (12 subjects for each race) received a single oral dose of memantine at 5 mg or 10 mg in the fasted state, followed by a washout period of ≥21 days, and then received a single oral dose of 20 mg of memantine in the fasted state. The mean t_{max} following the administration of any of the three doses of memantine in Japanese and Caucasian subjects ranged from 2.5 to 3.5 hours and from 4.0 to 5.0 hours, respectively. At 5mg, 10mg, and 20mg of memantine, the C_{max} was 6.777 ± 0.799 (mean ± SD), 15.207 ± 2.153, and 31.730 ± 4.514 ng/mL, respectively, in Japanese subjects and 4.612 ± 0.966, 9.072 ± 1.370, and 19.278 ± 4.770 ng/mL, respectively, in Caucasian subjects; the AUC_{∞} was 462.2 ± 85.9, 1370.7 ± 115.7, and 2490.4 ± 334.6 ng·h/mL, respectively, in Japanese subjects and 419.7 ± 86.6, 845.7 ± 128.5, and 1675.4 ± 344.7 ng·h/mL, respectively, in Caucasian subjects; and the mean $t_{1/2}$ was 61.50, 82.15, and 75.42 hours, respectively, in Japanese subjects and 64.73, 67.92, and 65.64 hours, respectively, in Caucasian subjects. The cumulative urinary excretion of memantine over the first 72 hours after administration was 30.467% to 34.109% in Japanese subjects and 29.283% to 32.509% in Caucasian subjects.

In Japanese and Caucasian subjects after the single dose of memantine at 20 mg, the plasma concentration of the N-gludantan conjugate was 6.787 ± 3.534 (mean ± SD) and 6.416 ± 3.228 ng/mL, respectively, at 2 hours post-dose and 0.737 ± 0.626 and 0.580 ± 0.588 ng/mL, respectively, at 72 hours post-dose. The 6-OH metabolite was detected in a trace amount, but declined to below the quantitation limit (< 1 ng/mL) at and after 10 hours post-dose in Japanese subjects, while it remained below the quantitation limit at all time points in Caucasian subjects. The 4-OH metabolite remained below the quantitation limit at all time points in Japanese and Caucasian subjects. The cumulative urinary excretion (percentage to the dose) of the N-gludantan conjugate, 6-OH metabolite, and the 4-OH metabolite during the 72 hours after the single dose of 20 mg was 2.193%, 1.100%, and 0.422%, respectively, in Japanese subjects and 2.278%, 1.304%, and 0.562%, respectively, in Caucasian subjects.

The concentration* of memantine in tear fluid following the single dose of 5, 10, and 20 mg was 12.432 ± 9.069 (mean ± SD), 38.387 ± 28.015, and 49.794 ± 15.654 ng/mL, respectively, at 4 hours post-dose and 10.008 ± 12.193, 25.905 ± 14.048, and 24.051 ± 11.242 ng/mL, respectively, at 48 hours post-dose in Japanese subjects and 9.228 ± 10.110, 36.270 ± 42.985, and 53.035 ± 37.577 ng/mL, respectively, at 4 hours post-dose and 0 (below the quantitation limit in all the subjects), 5.178 ± 8.305, and 30.165 ±

* Means and standard deviations were calculated with the values below the quantitation limit rounded to 0.

14.533 ng/mL, respectively, at 48 hours post-dose in Caucasian subjects. The tear fluid to plasma concentration ratio at 4 and 48 hours post-dose was 1.876 to 2.851 and 1.607 to 3.637, respectively, in Japanese subjects and 2.045 to 4.200 and 0.000 to 2.815, respectively, in Caucasian subjects.

4.(ii).A.(4) Studies in patients

4.(ii).A.(4).1) Japanese multiple-dose study in patients with AD (a) (5.3.3.2.1, Study IE2201)

Memantine was orally administered to Japanese patients with AD once daily after breakfast for 24 weeks, first at a dose of 5 mg, which was titrated in weekly increments of 5 mg to 10 or 20 mg as the maintenance dose. The concentration of memantine in plasma reached the steady state at Week 4, and the mean plasma memantine concentrations at Weeks 4, 8, 12, and 24 at dose levels of 10 and 20 mg ranged from 64.769 to 69.755 ng/mL and from 112.939 to 127.830 ng/mL, respectively (n = 10-12/time point). The concentrations of the N-gludantan conjugate, the 4-OH metabolite, and the 6-OH metabolite in plasma after 24 weeks of multiple doses at 20 mg were 16.814, 1.900, and 2.793 ng/mL, respectively.

The mean concentration of memantine in spinal fluid after 20 to 24 weeks of multiple doses at 10 and 20 mg was 43.260 and 73.999 ng/mL, respectively, and the spinal fluid to plasma concentration ratio of memantine was 0.63 and 0.72, respectively. Memantine metabolites detected in spinal fluid at Weeks 20 to 24 included only the N-gludantan conjugate and the 6-OH metabolite in 1 subject each, both around their quantitation limits (0.879 and 1 ng/mL, respectively).

4.(ii).A.(4).2) Japanese multiple-dose study in patients with AD (b) (5.3.5.1.1, Study IE2101 [double-blind phase])

Memantine was orally administered to Japanese patients with AD once daily after breakfast for 24 weeks, first at a dose of 5 mg, which was titrated in weekly increments of 5 mg to 10 or 20 mg as the maintenance dose. The concentration of memantine in plasma after 24 weeks of multiple doses at 10 and 20 mg was 69.9 ± 22.3 (mean ± SD) and 149.2 ± 45.3 ng/mL, respectively.

4.(ii).A.(4).3) Excretion in tear fluid during multiple doses (5.3.2.3.1)

Excretion of memantine in tear fluid was evaluated in Japanese patients with AD who received multiple doses of memantine at 20 mg. Tear fluid was collected from a total of 10 subjects, after 28 weeks in the extended open-label phase in the late phase II study (Study IE2101) and at ≥24 weeks after the start of memantine treatment in the long-term study (Study IE2301), and the volume of collected tear fluid was sufficient for quantitation in 5 subjects. In these 5 subjects, the concentrations of memantine in tear fluid and plasma were 395.19 ± 134.03 (mean ± SD) and 125.76 ± 28.52 ng/mL, respectively, and the transfer ratio from plasma to tear fluid (tear fluid/plasma concentration) was 3.2 ± 1.2.

4.(ii).A.(4).4) Population pharmacokinetic analysis (5.3.3.5.1)

Population pharmacokinetic (PPK) analysis was performed using the data on plasma concentrations of memantine administered to Japanese subjects in the following 5 studies: a phase III study (Study MA3301), a phase I study (Study IE1801), and clinical pharmacology studies (Studies IE1302, IE1601,

and IE2201). Studies IE1801, IE1302, IE2201, and IE1601 are summarized in "4.(ii).A.(2).1).(a) Japanese single-dose study," "4.(ii).A.(3).1) Single-dose study in healthy elderly Japanese and Caucasian subjects," "4.(ii).A.(4).1) Japanese multiple-dose study in patients with AD (a)," and "4.(ii).A.(5).1).(a) Pharmacokinetic study in Japanese patients with renal impairment," respectively. In Study MA3301, memantine was orally administered to 343 Japanese patients with AD once daily for 24 weeks at a starting dose of 5 mg, and the dose was titrated in weekly increments of 5 mg to 10 or 20 mg as the maintenance dose. Plasma was sampled for pharmacokinetic analysis at Weeks 12 and 24.

PPK analysis was performed using the plasma concentration data obtained from 427 subjects at 1726 time points. The major characteristics of the subjects included in the analysis were summarized as follows: age of 74 (21-92) years (median [minimum-maximum]), body weight of 52.0 (30.6-83.4) kg, creatinine clearance (Ccr) of 60 (11-133) mL/min, total bilirubin of 0.50 (0.20-1.90) mg/dL, AST of 21 (9-60) IU/L, alanine aminotransferase (ALT) of 15 (3-68) IU/L, alkaline phosphatase (ALP) of 232 (92-731) IU/L, and gamma-glutamyl transpeptidase (γ-GTP) of 18 (5-299) IU/L. In addition, urine pH was <5 in 0 subjects, 5 to 6 in 156 subjects, 6 to 7 in 172 subjects, and 7 to 8 in 99 subjects. The subjects consisted of 168 men and 259 women. The PPK of memantine was analyzed using a non-linear mixed effect model. A two-compartment model with first-order absorption without lag time was used as the basic model. Candidate covariates included Ccr, total bilirubin, AST, ALT, ALP, γ-GTP, and baseline urine pH (BpH), which were evaluated for their potential effects on the total body clearance of memantine (CL/F). Baseline body weight (Bweight) was evaluated for its potential effects on apparent distribution volume (V_d/F) as another covariate. As a result, significant covariates selected from these candidate covariates were Ccr and BpH for CL/F and Bweight for V_d/F, and were included in the final model. The details of the final model were as follows:

$$CL/F(L/h) = (7.07 + 1.06 \times (Ccr - 60) \times 60/1000) \times 0.866^{BpH} \times \exp(\eta_{CL/F})$$
$$V_d/F(L) = (688 + 5.70 \times (Bweight - 52))$$
$$Q/F(L/h) = 1.23$$
$$V_2/F(L) = 102$$
$$k_a(h^{-1}) = 1.22$$
$$Y = F \times \exp(\varepsilon_1) + \varepsilon_2$$

Q/F: Apparent intercompartmental clearance;
Ccr: Ccr at each time point;
Bweight: Baseline body weight;
BpH: Baseline urine pH (0 for urine pH of ≤7, 1 for urine pH of >7);
Y: Observed plasma drug concentration;
F: Predicted plasma drug concentration;
η: Interindividual variability with a mean of 0 and a variance of ω^2;
ε: Residual variability with a mean of 0 and a variance of σ^2

The estimated $\omega_{CL/F}^2$ was 0.0289 ± 0.00352 (mean ± standard error), and the estimated σ_1 and σ_2 were 0.239 ± 0.00990 and 0.203 ± 0.0588, respectively.

4.(ii).A.(5) Pharmacokinetic studies in special populations

4.(ii).A.(5).1) Patients with renal impairment

(a) Pharmacokinetic study in Japanese patients with renal impairment (5.3.3.3.1, Study IE1601)

A single oral dose of memantine at 10 mg was administered to the following Japanese subjects in the fasted state: 6 subjects with normal renal function (estimated Ccr of >80 mL/min), 6 subjects with mild renal impairment (estimated Ccr of ≥50 mL/min and ≤80 mL/min), 6 subjects with moderate renal impairment (estimated Ccr of ≥30 mL/min and <50 mL/min), and 7 subjects with severe renal impairment (estimated Ccr of ≥5 mL/min and <30 mL/min). In the subjects with normal renal function and those with mild, moderate, and severe renal impairment, the mean t_{max} was 6.2, 5.2, 4.3, and 5.4 hours, respectively; the C_{max} was 12.660 ± 2.137 (mean ± SD), 17.252 ± 3.944, 15.755 ± 3.698, and 15.826 ± 0.616 ng/mL, respectively; the AUC_∞ was 1045.8 ± 81.7, 1639.7 ± 180.0, 2071.3 ± 530.7, and 2437.0 ± 451.4 ng·h/mL, respectively; and the mean $t_{1/2}$ was 61.15, 83.00, 100.13, and 124.31 hours, respectively. The AUC_∞ and $t_{1/2}$ thus increased commensurately with the decrease in renal function. The mean plasma protein binding of memantine was 40.83%, 49.45%, 41.23%, and 31.77%, respectively.

(b) Pharmacokinetic study in foreign patients with renal impairment (5.3.3.3.2, Study MEM-PK-02 [reference data])

A single oral dose of memantine at 20 mg was administered to the following foreign subjects in the fasted state: 8 subjects with mild renal impairment (estimated Ccr of ≥50 mL/min and ≤80 mL/min), 8 subjects with moderate renal impairment (estimated Ccr of ≥30 mL/min and <50 mL/min), 8 subjects with severe renal impairment (estimated Ccr of ≥5 mL/min and <30 mL/min), and 8 subjects with normal renal function (estimated Ccr of >80 mL/min). The PK parameters in the subjects with mild, moderate, and severe renal impairment and those with normal renal function were as follows: the mean t_{max} was 7.0, 9.0, 8.3, and 7.6 hours, respectively; the C_{max} was 19.30 ± 2.65 (mean ± SD), 24.25 ± 2.41, 25.76 ± 9.46, and 22.08 ± 5.07 ng/mL, respectively; the AUC_∞ was 2024 ± 557, 3113 ± 729, 4167 ± 1083, and 1941 ± 397 ng·h/mL, respectively; and the mean $t_{1/2}$ was 76.1, 91.0, 126.0, and 64.6 hours, respectively.

4.(ii).A.(5).2) Pharmacokinetic study in foreign patients with hepatic impairment (5.3.3.3.3, Study MEM-PK-15)

A single oral dose of memantine at 20 mg was administered to the following foreign subjects in the fasted state: 8 subjects with moderate hepatic impairment (Child-Pugh grade B and Child-Pugh score of 7-9) and 8 subjects with normal hepatic function. The PK parameters in the subjects with moderate hepatic impairment and those with normal hepatic function as follows: the C_{max} was 21.06 ± 5.42 (mean ± SD) and 21.82 ± 5.35 ng/mL, respectively; the AUC_∞ was 2031.64 ± 759.00 and 2018.87 ± 332.75 ng·h/mL, respectively; and the $t_{1/2}$ was 81.91 ± 29.78 and 70.80 ± 18.66 hours, respectively. Moderate

hepatic impairment thus was not considered to affect the pharmacokinetics of memantine.

4.(ii).A.(6) Drug interactions

4.(ii).A.(6).1) Drugs affecting urine pH (5.3.3.4.2, Study MRZ90001-9601)

An open-label, 4-treatment, 4-period crossover study was conducted in 13 foreign healthy adult male subjects to evaluate the effects of urine pH and flow rate on the pharmacokinetics of memantine. Subjects received multiple oral doses of memantine at 10 mg for 43 days. The first 2 days of each week in the 4 weeks starting on Day 21 of memantine administration were designated weekly as Periods 1 through 4 (with a washout period of ≥5 days) for co-administration. In each Period, either ammonium chloride or sodium bicarbonate was co-administered in multiple doses to make urine pH either acidic or alkaline, and water intake was set at 600 mL/32 hours in the low urine flow rate group and 6000 mL/32 hours in the high urine flow rate group. Starting at 18 hours before the first pharmacokinetic sampling, ammonium chloride was administered every 3 hours at a dose of 1 g (12 doses in total) and sodium bicarbonate was administered every 4 hours at a dose of 4 g (9 doses in a total).

In the low and high flow rate acidic urine groups and the low and high flow rate alkaline urine groups, the median CL/F was 223.3, 234.3, 42.0, and 51.7 mL/min, respectively; the renal clearance was 210.2, 218.7, 19.4, and 30.5 mL/min, respectively; and the cumulative urinary excretion was 9.43, 9.77, 1.29, and 1.71 mg, respectively. The CL/F and renal clearance of memantine were 7- to 10-fold higher when urine was acidic than when it was alkaline. Similarly, the cumulative urinary excretion during the 24 hours after administration was 5.7- to 7.4-fold higher when urine was acidic than when urine was alkaline.

4.(ii).A.(6).2) Donepezil (5.3.3.4.3, Study MEM-PK-07)

A total of 24 foreign healthy adult subjects received a single oral dose of memantine at 10 mg on Day 1 in the fasted state, followed by once-daily oral administration of donepezil hydrochloride (hereinafter referred to as donepezil) at 5 mg on Days 15 to 21 and at 10 mg on Days 22 to 42 (in the fasted state on Day 42). On Day 43, they received 10 mg of memantine in combination with 10 mg of donepezil in the fasted state. While the pharmacokinetics of memantine was not affected by donepezil, memantine increased the mean C_{max} and AUC_{0-24} of donepezil by approximately 13% and 9%, respectively.

Concomitant use of memantine did not affect the inhibitory effect of donepezil on erythrocyte AChE.

4.(ii).A.(6).3) Hydrochlorothiazide-triamterene combination (5.3.3.4.5, Study 961201/Me. Me)

A total of 21 foreign healthy adult subjects received once-daily oral doses of one tablet containing a combination of hydrochlorothiazide (HCTZ) 25 mg and triamterene (TA) 50 mg on Days 1 to 4 and once-daily oral doses of memantine, at 5 mg on Days 5 to 7, at 10 mg on Days 8 to 11, and at 20 mg on Days 12 to 32 (in the fasted state on Days 4, 25, and 32). One HCTZ/TA combination tablet (containing 25 mg of HCTZ and 50 mg of TA) was co-administered with memantine on Days 26 to 32. The HCTZ/TA combination drug did not affect the pharmacokinetics of memantine. Memantine did not

affect the pharmacokinetics of TA and its hydroxylated metabolite, but decreased the mean C_{max} and $AUC_{0\text{-}24}$ of HCTZ by approximately 19% and 20%, respectively.

Furthermore, memantine was examined for its interaction with warfarin, Glucovance (a combination drug of glibenclamide 1.25 mg and metformin hydrochloride 250 mg), and bupropion hydrochloride (not approved in Japan). No interaction was detected between memantine and any of these drugs.

4.(ii).B Outline of the review by PMDA

4.(ii).B.(1) Effects of pharmacokinetic differences between Japanese and foreign populations

Taking into account that the C_{max} and AUC_{∞} of memantine in Japanese healthy adult male subjects were 1.48- and 1.29-fold, respectively, higher than those in foreign healthy adult male subjects; that its plasma concentrations in elderly individuals or patients with AD was also higher in the Japanese population than in foreign populations; and that the efficacy of memantine in terms of overall clinical status, which had been shown in foreign studies, was not verified in Japanese clinical studies [see "4.(iii) Summary of clinical efficacy and safety"], PMDA asked the applicant to discuss how differences in plasma memantine concentrations affect the efficacy and safety of memantine, and to provide a rationale for introducing into Japan the same dose level as used outside Japan.

The applicant explained as follows:

In a late phase II study (Study IE2101 [double-blind phase]), the efficacy of memantine was evaluated using the "severe impairment battery-Japanese version (SIB-J)" and the "Clinician's interview-based impression of change plus Japanese version (CIBIC plus-J)," and the results were better in the 20 mg group than in the 10 mg group. Study IE2101 (double-blind phase) and a phase III study (Study IE3501) investigated the relationship between the efficacy of memantine and its plasma concentrations, and showed no trends suggesting an association between an increase in the plasma concentration and a reduction in the efficacy. Therefore, the higher plasma memantine concentrations in Japanese patients with AD than in foreign patients with AD are considered unlikely to have an effect on its efficacy in Japanese patients.

A comparison between the pooled data from Japanese and foreign double-blind comparative studies in terms of the incidence of adverse events during treatment with memantine at 20 mg revealed no major differences between these 2 populations, with the incidence being 79.3% (413 of 521 subjects) in Japanese subjects and 71.8% (892 of 1242 subjects) in foreign subjects. The pooled data of Japanese double-blind comparative studies (pooled results from IE2101 [double-blind phase], IE2201, IE3501, and MA3301) was analyzed in subgroups based on the steady state plasma concentration of memantine, divided in increments of 50 ng/mL. The incidence of adverse events was 100% (10 of 10 subjects) in the subgroup with a plasma concentration of ≥250 ng/mL, but was 72.6% (77 of 106 subjects) in the <50 ng/mL subgroup, 80.4% (242 of 301 subjects) in the ≥50 to <100 ng/mL subgroup, 79.1% (182 of 230 subjects) in the ≥100 to <150 ng/mL subgroup, 75.0% (78 of 104 subjects) in the ≥150 to <200 ng/mL subgroup, and 72.1% (31 of 43 subjects) in the ≥200 to <250 ng/mL subgroup, with no major

differences in the incidence of adverse events between the <250 ng/mL subgroups and the placebo group (77.2%, 399 of 517 subjects). No differences have thus been shown in the overall incidence of adverse events stratified by plasma memantine concentrations or in the incidence of individual events among the Japanese population when the plasma concentration of memantine was <250 ng/mL.

The above results indicate that the efficacy and safety of memantine are unlikely to be affected by differences in plasma concentrations between Japanese and foreign populations. Therefore, it is considered appropriate to introduce into Japan the same maintenance dose of 20 mg/day as used outside Japan.

PMDA considers as follows:
Taking into account that Study IE2101 (double-blind phase) identified no trends suggesting a relationship between higher plasma concentrations of memantine and its reduced efficacy; that there were no notable differences in the incidence of adverse events between Japanese and foreign patients with AD; and that the pooled data of Japanese double-blind comparative studies showed no obvious differences in the incidence of adverse events related to plasma memantine concentration when the concentration was <250 ng/mL, the difference observed in plasma concentrations between Japanese and foreign populations is not grounds to reject the dose proposed for registration in Japan, which is the same as the dose used outside Japan.

4.(ii).B.(2) Pharmacokinetic differences between once-daily and twice-daily administration
The applicant provided the following explanations for the difference in regimen of memantine between Japan and other countries:
While the regimen approved outside Japan is twice-daily administration at a dose level of 20 mg/day, pharmacokinetic properties of memantine (t_{max} and $t_{1/2}$, approximately 6 and 70 hours, respectively) suggest that a once-daily regimen is unlikely to differ significantly from a twice-daily regimen in terms of time course of plasma memantine concentrations in long-term treatment. Prior to the conduct of Japanese clinical studies of memantine, changes in plasma concentrations over time in healthy elderly foreign subjects were simulated for once-daily and twice-daily 20 mg/day dosing regimens based on the plasma concentrations following a single oral dose. Since the simulated plasma concentration time curves were generally the same between the 2 regimens, the once-daily regimen was used in all of the Japanese clinical studies. Given that no particular problem has arisen from this regimen, once-daily dosing has been proposed as the memantine regimen in Japan.

PMDA acknowledged the validity of the once-daily dosing regimen employed in Japanese clinical studies and of the proposed once-daily regimen based on the results of these studies.

4.(ii).B.(3) Dosing to patients with moderate renal impairment
Taking into account that the AUC_{∞} was about 2-fold higher in Japanese patients with moderate renal impairment than in subjects with normal renal function, PMDA asked the applicant to discuss whether

or not the caution statement advising dose adjustment in patients with severe renal impairment (estimated Ccr of <30 mL/min) in the draft package insert should be extended to include patients with moderate renal impairment.

The applicant explained as follows:
Although the AUC_{∞} was about 2-fold higher in Japanese patients with moderate renal impairment than in subjects with normal renal function in Study IE1601, no differences were observed in the incidence of adverse events stratified by plasma memantine concentrations, as presented in 4.(ii).B.(1), when the plasma memantine concentration was <250 ng/mL, a level more than 2-fold the plasma level in subjects with normal renal function who received memantine at 20 mg/day. Among subjects in Japanese double-blind studies stratified by Ccr into subgroups with mild, moderate, and severe renal impairment and with normal renal function, the incidence of adverse events was 78.0% (347 of 445 subjects), 78.2% (190 of 243 subjects), 85.2% (23 of 27 subjects), and 77.2% (88 of 114), respectively, in the memantine 20 mg group and 77.3% (218 of 282 subjects), 77.2% (112 of 145 subjects), 83.3% (15 of 18 subjects), and 74.6% (53 of 71 subjects), respectively, in the placebo group, with no memantine-placebo differences in any subject stratum. Taking into account that evaluation in patients with severe renal impairment was insufficient in Japanese double-blind comparative studies due to their small population size, and that a maintenance dose of 10 mg/day has been selected for patients with severe renal impairment in Europe and the US, a similar precaution for use in patients with severe renal impairment should be considered necessary in Japan. Therefore, a caution statement has been included in the "Precautions for Dosage and Administration" section in the proposed package insert. However, given that general considerations for patients with renal impairment are provided in the "Careful Administration" section, inclusion of patients with moderate renal impairment in the caution statement currently provided for patients with severe renal impairment should be considered unnecessary.

PMDA considered as follows:
Taking account of the applicant's explanations that patients with moderate renal impairment enrolled in Japanese double-blind comparative studies posed no particular safety concern and did not require any dose adjustment, and that in an analysis of subgroups based on the steady state plasma concentration of memantine, divided in increments of 50 ng/mL, the incidence of adverse events was not affected by the difference in plasma memantine concentrations when the concentration was <250 ng/mL, there is little necessity to adjust the dosage regimen of memantine for patients with moderate renal impairment. The appropriateness of the caution statements for patients with renal impairment will be determined, taking account of comments from the Expert Discussion.

4.(ii).B.(4) Dosage and administration in patients with severe renal impairment

The results of Study IE1601 and Study MEM-PK-02 showed a delay in renal excretion and an increase in blood concentrations of memantine depending on the degree of renal function deterioration. In the Japanese double-blind comparative study, evaluation in patients with severe renal impairment was insufficient due to the small size of the patient population. The maintenance dose in patients with severe

renal impairment is 10 mg in the EU and the US. Consequently, the following caution statement has been proposed in Japan concerning the dosage and administration in patients with severe renal impairment: "This drug product should be administered with caution in patients with severe renal impairment under clinical monitoring, for example, by using a reduced maintenance dose of 10 mg once daily." Then, PMDA asked the applicant whether or not memantine is expected to be effective at a maintenance dose of 10 mg in patients with severe renal impairment.

The applicant explained that, although no data are available on the efficacy of memantine at a maintenance dose of 10 mg in patients with severe renal impairment, a time-course simulation of plasma memantine concentrations in patients with renal impairment based on the data from Study IE1601 indicated that the steady-state plasma memantine concentration was higher in patients with severe renal impairment after administration of 10 mg than in individuals with normal renal function after administration of 20 mg. Therefore, memantine is expected to be effective even at 10 mg in patients with severe renal impairment.

PMDA considers as follows:
The applicant's following explanation is reasonable: No data are available for the efficacy of memantine at 10 mg in patients with severe renal impairment; however, based on the results of Study IE1601, memantine can be expected to have similar efficacy in patients with severe renal impairment at a maintenance dose of 10 mg to that in individuals with normal renal function at a maintenance dose of 20 mg. Therefore, it is appropriate to select a maintenance dose of 10 mg in Japan, as with the dosage regimen approved in foreign countries, for patients with severe renal impairment. Nevertheless, a final decision on the appropriateness of the details of the caution statement will be made, taking account of comments from the Expert Discussion.

4.(ii).B.(5) Dose titration interval for patients with renal impairment

Given that a simulation of multiple doses of memantine based on the data from Study IE1601 showed that plasma memantine concentrations remained higher in subjects with renal impairment than in those with normal renal function, PMDA asked the applicant to explain whether or not patient safety would be ensured by specifying a dose titration interval of one week for all patients including those with renal impairment, based on the safety information for subjects with renal impairment obtained during the dose titration period in clinical studies.

The applicant explained as follows:
There were no Ccr-related differences in the incidence of adverse events among subjects in the memantine group at Week 4 during the dose titration period. Of adverse drug reactions that occurred during the dose titration period in the memantine group, nervous system disorders (mainly dizziness) occurred at a slightly higher incidence in subjects with moderate renal impairment at Week 3. However, none of these events were serious and the majority of subjects were able to continue receiving treatment. Based on these results, a one-week dose titration interval is considered applicable also to patients with

renal impairment, although the incidence of dizziness in patients with moderate renal impairment was high.

PMDA accepted the applicant's response.

4.(ii).B.(6) Effects of gender-related differences in pharmacokinetics of memantine

Given that the C_{max} and $AUC_{24,ss}$ were higher in female subjects than in male subjects by 48% and 47%, respectively, in a phase I study (Study MRZ90001-9704), and that a gender-related difference was observed in rats in terms of transfer of memantine to the brain [see "3.(ii).B.(2) Gender-related differences in transfer to the brain in rats"], PMDA asked the applicant to explain the effects of gender-related differences in pharmacokinetics on the efficacy and safety of memantine, and the possibility that there could be gender-related differences in transfer of memantine to the brain and in effects on the central nervous system when memantine is administered to humans.

The applicant explained as follows:

In a subgroup analysis on changes in the SIB-J score used for the evaluation of cognitive function in the phase III study (Study IE3501), scores in both male subjects and female subjects were higher in the memantine group than in the placebo group, with pharmacokinetic gender-related differences having no demonstrable effect on the efficacy of memantine. Regarding safety, the incidence of adverse events in Japanese double-blind studies was higher in male subjects (84.8% [229 of 270 subjects]) than in female subjects (75.0% [419 of 559 subjects]). Regarding effects on the central nervous system, the incidences of nervous system disorders and psychiatric disorders were 13.3% (36 of 270 subjects) and 12.2% (33 of 270 subjects), respectively, in male subjects and 14.5% (81 of 559 subjects) and 10.4% (58 of 559 subjects), respectively, in female subjects, with no gender-related differences shown.

When memantine was administered to patients with AD for 24 weeks, the concentration in spinal fluid at Weeks 20 to 24 was 40.570 ± 5.044 ng/mL (mean ± SD) in male subjects and 47.968 ± 13.931 ng/mL in female subjects in the 10 mg group and 74.733 ± 15.061 ng/mL in male subjects and 72.530 ± 23.052 ng/mL in female subjects in the 20 mg group, with no gender-related differences shown in memantine concentrations in spinal fluid.

These results are interpreted as indicating that the gender-related differences in pharmacokinetics of memantine have no effects on its efficacy and safety, and that there are no gender-related differences in transfer of memantine to the brain and in the effects on the central nervous system when memantine is administered to humans.

PMDA accepted the applicant's response and considered that the gender-related differences in pharmacokinetics of memantine are unlikely to be of clinical concern.

4.(ii).B.(7) Necessity of advising caution about ocular toxicity

Memantine has been found to have an affinity for melanin, and its distribution into the eyes of pigmented rats has been reported in non-clinical studies. After multiple doses in humans, the concentration of memantine in tear fluid was 2.0- to 4.7-fold that in plasma, and eye disorders have been reported as serious adverse events in Japanese clinical studies. Therefore, PMDA asked the applicant to explain the necessity of providing a caution statement regarding the ocular toxicity of memantine.

The applicant explained as follows:
A 6-week dietary administration toxicity study in albino and pigmented rats showed corneal malformation, keratitis, localized lens opacity, and histological changes of the cornea occurring after administration at ≥120 mg/kg/day. Although the high concentrations of memantine in the cornea and tear fluid may have been related to the pathological changes, memantine concentrations in tear fluid in rats and dogs with no ocular lesions (corneal lesions) treated at the maximum doses (80 mg/kg/day and 9 mg/kg/day, respectively) were approximately 63- and 2-fold, respectively, those in tear fluid in patients treated for ≥24 weeks at 20 mg/day. Therefore, eye disorders are unlikely to occur at clinical doses.

Because Japanese clinical studies (all studies used for safety analysis) reported similar incidences of eye disorders as adverse events for both the placebo group (5.2% [27 of 517 subjects]) and the memantine group (6.3% [52 of 829 subjects]), these results were not considered to be of concern. In Japanese clinical studies (Studies IE3501, MA3301, IE2201, and MA3302), ophthalmologic examination by slit-lamp biomicroscopy showed no relevant problems in the cornea or lens. Serious eye disorders reported in Japanese clinical studies included 13 events in 10 of 1115 subjects in the memantine group (cataract in 7 subjects, glaucoma in 3 subjects, and angle closure glaucoma, retinal vein occlusion and retinal detachment in 1 subject each) and no events in the placebo group. Cataract and glaucoma pre-existed prior to the study in 7 and 3 subjects, respectively. Given that cataract and glaucoma are specific to the elderly population, their progression during long-term observation and subsequent indication for surgery were considered to be the basis on which the events were assessed to be serious.

Based on the above reasoning, the applicant considered that no caution about ocular toxicity is necessary.

PMDA accepted the applicant's response based on the following findings: (i) in Japanese clinical studies, no corneal or lenticular problems were found by ophthalmologic examination by slit-lamp biomicroscopy performed to follow up on pathological ocular changes observed in non-clinical toxicity studies; (ii) Japanese clinical studies showed no marked difference in the incidence of eye disorders between the placebo and memantine groups; and (iii) no particular caution is advised in foreign countries where considerable clinical experience on the use of memantine has been accumulated.

4.(ii).B.(8) Drug interactions that may affect renal excretion of memantine

PMDA asked the applicant to explain why the renal clearance of memantine decreases when the urine is alkaline, particularly in regard to the relationship with the mechanism of urinary excretion of

memantine, e.g., any involvement of transporters; and whether or not there are any drugs that may affect the renal excretion of memantine, other than "urine-alkalinizing drugs" and "drugs excreted by renal tubular secretion (cation transport system)."

The applicant explained as follows:
In Study MRZ90001-9601 performed to evaluate the effect of urine pH, the pH of acidic urine and alkaline urine was approximately 5 and 8, respectively. Since the dissociation constant (pKa) of memantine is 10.58, the proportion of the undissociated form at pH 5 and pH 8 was calculated to be 0.0003% and 0.3%, respectively. According to the pH-partition hypothesis, alkalinization of urine markedly increases the proportion of the more membrane-permeable undissociated form of weakly basic drugs such as memantine, and thereby enhances renal tubular reabsorption with a decrease in renal clearance. Meanwhile, memantine is secreted from blood into the renal tubule by an organic cation transporter (OCT2) localized to the tubular basolateral membrane (Busch AE, et al. *Mol Pharmacol*. 1998;54:342-52). Since blood pH does not change significantly even if urine pH changes, tubular secretion by OCT2 is unlikely to be affected by urine pH. Renal tubular reabsorption of memantine is likely to be mediated by simple diffusion. Therefore, interactions with any drugs other than urine-alkalinizing agents are unlikely to occur.

Based on the above mechanism, renal excretion of memantine is considered unlikely to be affected by any drugs other than "drugs excreted by the cation transport system" and "urine-alkalinizing drugs."

PMDA accepted the applicant's response.

4.(iii) Summary of clinical efficacy and safety

In the development of memantine in Japan, a Japanese late phase II study (Study IE2101 [double-blind phase]) was conducted as a bridging study to extrapolate data from a foreign phase III study (Study MRZ90001-9605 [double-blind phase]), taking into account that the development of mementine had been started earlier in foreign countries than in Japan. However, no similarity was demonstrated in terms of efficacy between the results of the Japanese and foreign studies, and therefore, the Japanese study was considered to have failed to meet the requirements for serving as a bridging study. Subsequently, a Japanese phase III study (Study IE3501) was conducted to investigate the efficacy and safety of memantine in the Japanese population.

4.(iii).A Summary of the submitted data

As the evaluation data, the results from the following 26 studies were submitted: Japanese studies including 6 clinical pharmacology studies (including 1 multiregional study), 3 phase II studies, 2 phase III studies, 1 general clinical study, and 3 long-term studies, and foreign studies including 8 clinical pharmacology studies and 3 phase III studies [for BE and pharmacokinetics, see "4.(i) Summary of biopharmaceutic studies and associated analytical methods" and "4.(ii) Summary of clinical pharmacology studies"]. The major results of the studies are shown below.

4.(iii).A.(1) Japanese phase I studies

4.(iii).A.(1).1) BE study between 5 mg and 10 mg tablets (5.3.1.2.1; Study IE1301; Studied period, ■ 20■ to ■ 20■)

The BE between the 5 mg and 10 mg tablets of memantine was investigated at 1 center in Japan in an open-label, 2-treatment, 2-period, crossover study enrolling 18 Japanese healthy adult male subjects. Subjects received a single oral dose of four 5 mg tablets or two 10 mg tablets in the fasted state (with a washout period of 21 days).

Adverse events occurred in 2 subjects (feeling abnormal in 1 subject, and feeling abnormal/somnolence/pharyngolaryngeal pain/pharyngeal erythema/rhinorrhoea/cough in 1 subject) after the administration of 5 mg tablets, but no events occurred after the administration of 10 mg tablets. These events were all mild in severity and resolved without treatment. No deaths or serious adverse events were reported.

There were no abnormal changes or findings in laboratory test results, vital signs, or electrocardiogram (ECG).

4.(iii).A.(1).2) BE study between 10 mg and 20 mg tablets (5.3.1.2.2; Study IE1602; Studied period, ■ 20■ to ■ 20■)

The BE between the 10 mg and 20 mg tablets of memantine was investigated at 1 center in Japan in an open-label, 2-treatment, 2-period, crossover study enrolling 18 Japanese healthy adult male subjects. Subjects received a single oral dose of two 10 mg tablets or one 20 mg tablet in the fasted state (with a washout period of 21 days).

Adverse events occurred in 2 subjects (abnormal faeces and nasopharyngitis) after the administration of 10 mg tablets and in 6 subjects (nasopharyngitis in 2 subjects, and abnormal faeces, influenza, protein urine present, and rhinitis allergic in 1 subject each) after the administration of one 20 mg tablet. Influenza and nasopharyngitis in 1 subject each were moderate and all the other events were mild in severity. No deaths or serious adverse events were reported.

After the administration of one 20 mg tablet, abnormal changes were observed in laboratory test results in 3 subjects and in vital signs in 1 subject. These abnormal changes were caused by the reported adverse events. There were no abnormal ECG findings.

4.(iii).A.(1).3) Single oral dose study in healthy adults (5.3.3.1.1; Study IE1801; Studied period, ■ 19■ to ■ 19■)

The safety and pharmacokinetics of a single dose of memantine was investigated at 1 center in Japan in a placebo-controlled, single-blind study enrolling 32 Japanese healthy adult male subjects. Subjects received a single oral dose of memantine at 5, 10, 20, or 40 mg (6 subjects per dose group) or placebo

(8 subjects) in the fasted state.

The incidence of adverse events was 50.0% (4 of 8 subjects) in the placebo group, 50.0% (3 of 6 subjects) in the memantine 5 mg group, 50.0% (3 of 6 subjects) in the memantine 10 mg group, 66.7% (4 of 6 subjects) in the memantine 20 mg group, and 100% (6 of 6 subjects) in the memantine 40 mg group. The adverse events reported in ≥2 subjects in any group were sleepiness (1, 0, 1, 3, and 6 subjects in the placebo, memantine 5 mg, 10 mg, 20 mg, and 40 mg groups, respectively), dizziness (0, 0, 0, 0, and 6 subjects, respectively), lightheadedness (0, 1, 0, 0, and 5 subjects, respectively), feelings of weakness (0, 0, 0, 0, and 2 subjects, respectively), and skin eruption (0, 0, 0, 2, and 1 subjects, respectively). No deaths or serious adverse events were reported.

There were no clinically relevant changes or abnormal findings in laboratory test results, vital signs, ECG, brain waves, ophthalmologic examination, or renal function test.

4.(iii).A.(1).4) Pharmacokinetic study in patients with renal impairment (5.3.3.3.1; Study IE1601; Studied period, [redacted] 20[redacted] to [redacted] 20[redacted])

The pharmacokinetics of a single oral dose of memantine at 10 mg administered in the fasted state was investigated at 7 centers in Japan to compare subjects with mild to severe renal impairment to those with normal renal function in an open-label study enrolling 25 Japanese subjects (6 subjects with normal renal function [estimated Ccr of >80 mL/min], 6 subjects with mild renal impairment [estimated Ccr of ≥50 mL/min to ≤80 mL/min], 6 subjects with moderate renal impairment [estimated Ccr of ≥30 mL/min to <50 mL/min], and 7 subjects with severe renal impairment [estimated Ccr of ≥5 mL/min to <30 mL/min]).

The incidence of adverse events was 16.7% (1 of 6 subjects) in the normal renal function group, 50.0% (3 of 6 subjects) in the mild renal impairment group, 50.0% (3 of 6 subjects) in the moderate renal impairment group, and 71.4% (5 of 7 subjects) in the severe renal impairment group. There were no adverse events reported in ≥2 subjects in any group. No deaths or serious adverse events were reported.

There were no clinically meaningful changes or abnormal findings in laboratory test results, vital signs, or ECG, except for blood glucose increased in 1 subject in the severe renal impairment group and pyrexia and blood pressure increased in 1 subject each (the same subject) in the moderate renal impairment group.

4.(iii).A.(2) Foreign phase I studies

4.(iii).A.(2).1) Pharmacokinetic study in patients with hepatic impairment (5.3.3.3.3; Study MEM-PK-15; Studied period, [redacted] 20[redacted] to [redacted] 20[redacted])

The pharmacokinetics of a single oral dose of memantine at 20 mg administered in the fasted state was investigated at 1 foreign center to compare subjects with normal hepatic function to those with moderate hepatic impairment in an open-label study enrolling 16 foreign subjects (8 subjects with normal hepatic

function and 8 subjects with moderate hepatic impairment [Child-Pugh grade B, Child-Pugh score of 7 to 9]).

The incidence of adverse events was 37.5% (3 of 8 subjects) in the normal hepatic function group and 50.0% (4 of 8 subjects) in the moderate hepatic impairment group. The only adverse event reported in ≥2 subjects in either group was headache (1 subject in the normal hepatic function group and 2 subjects in the hepatic impairment group). No deaths or serious adverse events were reported.

There were no clinically meaningful changes or abnormal findings in laboratory test results, vital signs, or ECG.

4.(iii).A.(2).2) Study on the effects of urine pH (5.3.3.4.2; Study MRZ90001-9601; Studied period, [redacted] 19[redacted] to [redacted] 19[redacted])

An open-label, 4-treatment, 4-period, crossover study was conducted in 13 foreign healthy adult male subjects at 1 foreign center (with a washout period of ≥5 days) to evaluate the effects of urine pH and flow rate on the pharmacokinetics of memantine. Subjects received multiple oral doses of memantine at 10 mg during the period of 43 days. The first 2 days of each week in the 4 weeks starting on Day 21 of memantine administration were designated weekly as Periods 1 through 4. In each Period, either ammonium chloride or sodium bicarbonate was co-administered in multiple doses to make urine pH either acidic or alkaline, and water intake was adjusted to make the urine flow rate low or high. One subject was withdrawn from the study due to an adverse event (insomnia).

The incidence of adverse events was 15.4% (2 of 13 subjects), and headache and insomnia occurred in 1 subject each. No deaths or serious adverse events were reported.

There were no clinically meaningful changes in laboratory test results.

4.(iii).A.(2).3) Drug interaction study with donepezil (5.3.3.4.3; Study MEM-PK-07; Studied period, [redacted] 20[redacted] to [redacted] 20[redacted])

The pharmacokinetic interactions between memantine and donepezil and the effects of memantine on the inhibition of AChE by donepezil were investigated at 1 foreign center in an open-label study enrolling 24 foreign healthy adult subjects. Subjects received a single oral dose of memantine at 10 mg in the fasted state on Day 1, followed by a 14-day washout period, and then received multiple once-daily oral doses of donepezil, at 5 mg for 7 days (from Day 15 to Day 21) and at 10 mg for 22 days (from Day 22). On Day 43, memantine 10 mg was co-administered with donepezil 10 mg. Five subjects were withdrawn from the study, and the reasons included adverse events during the donepezil administration in 2 subjects, and consent withdrawal, poor compliance, and loss to follow-up in 1 subject each.

The incidence of adverse events was 8.3% (2 of 24 subjects) after the administration of memantine alone,

86.4% (19 of 22 subjects) during the administration of donepezil alone, and 31.6% (6 of 19 subjects) after the co-administration of memantine and donepezil. The adverse events reported in ≥3 subjects were queasy (0 subjects after the administration of memantine alone, 13 subjects during the administration of donepezil alone, and 0 subjects after the co-administration of the two drugs), headache (2, 8, and 3 subjects, respectively), light-headed feeling (0, 8, and 0 subjects, respectively), dizziness (0, 7, and 3 subjects, respectively), vomiting (0, 7, and 0 subjects, respectively), general weakness (0, 4, and 0 subjects, respectively), diarrhoea (0, 4, and 0 subjects, respectively), and fatigue (0, 3, and 0 subjects, respectively). No deaths or serious adverse events were reported.

There were no clinically meaningful changes or abnormal findings in laboratory test results, vital signs, or ECG.

4.(iii).A.(2).4) Drug interaction study with diuretics (5.3.3.4.5; Study 961201/Me. Me; Studied period, [redacted] 19[redacted] to [redacted] 19[redacted])

The pharmacokinetic drug interactions of memantine and the HCTZ/TA combination drug were investigated at 1 foreign center in an open-label study enrolling 21 foreign healthy adult subjects. Subjects received once-daily oral doses of one HCTZ 25 mg / TA 50 mg combination tablet on Days 1 to 4, and then received multiple once-daily oral doses of memantine at 5 mg on Days 5 to 7, at 10 mg on Days 8 to 11, and at 20 mg on Days 12 to 32. One HCTZ 25 mg / TA 50 mg combination tablet was co-administered with memantine on Days 26 to 32 (in the fasted state on Days 4, 25, and 32). One subject was withdrawn from the study due to an adverse event (gastritis).

The incidence of adverse events was 90.5% (19 of 21 subjects), and the adverse events reported in ≥3 subjects were dizziness in 10 subjects, numbness in 7 subjects, headache in 7 subjects, and fatigue in 3 subjects. No deaths or serious adverse events were reported. The only adverse event leading to study drug discontinuation was gastritis reported in 1 subject during the administration of memantine alone.

There were no clinically relevant findings in laboratory test results or vital signs.

4.(iii).A.(3) Japanese and foreign phase I studies (5.3.3.3.4, Study IE1302 Studied period, [redacted] 20[redacted] to [redacted] 20[redacted] [Japan]; [redacted] 20[redacted] to [redacted] 20[redacted] [France])

The pharmacokinetics and safety of memantine in the elderly Japanese and Caucasian populations were investigated at 2 centers in and outside Japan in an open-label study enrolling 24 healthy adult male subjects aged ≥65 years (12 Japanese and 12 Caucasian subjects). Subjects received a single oral dose of memantine at 5 or 10 mg in the fasted state (6 Japanese and 6 Caucasian subjects per dose group, Period 1), followed by a 21-day washout period (23 to 29 days for Caucasian subjects), and then received a single oral dose of memantine at 20 mg in the fasted state (Period 2). One Japanese subject and 1 Caucasian subject were withdrawn from the study due to adverse events before entering Period 2.

Adverse events were reported in 1 Japanese subject (ALT increased/AST increased/γ-GTP increased)

after the 5-mg dose, 1 Japanese subject (rash/pruritus) after the 10-mg dose, 2 Caucasian subjects (oedema peripheral and conjunctivitis) after the 5-mg dose, 2 Caucasian subjects (dizziness/ventricular extrasystoles/pollakiuria and rhinitis) after the 10-mg dose, and 4 Caucasian subjects (oedema peripheral, venipuncture site haemorrhage/hand fracture, loose stools, and rhinitis) after the 20-mg dose. One Japanese subject who experienced rash and pruritus at 10 mg and 1 Caucasian subject who experienced ventricular extrasystoles at 10 mg were withdrawn from the study. No deaths or serious adverse events were reported.

There were no clinically relevant changes in laboratory test results, vital signs, or ECG except for the above-mentioned events (ALT increased/AST increased/γ-GTP increased and ventricular extrasystoles) in 2 subjects.

4.(iii).A.(4) Japanese phase II studies

4.(iii).A.(4).1) Japanese early phase II study (5.3.5.2.1; Study IE2901; Studied period, [redacted] 20[redacted] to [redacted] 20[redacted])

The efficacy and safety of multiple oral doses of memantine at 10 or 20 mg in patients with severe AD were explored at 36 centers in Japan in an open-label, comparative, parallel-group study enrolling Japanese patients with AD (target sample size of 60 subjects, 30 subjects in each group).

Patients received memantine once daily after breakfast (if missed, the dose was taken no later than 14:00 on the same day) for 12 weeks, at a daily dose titrated from 5 mg to the maintenance dose (10 or 20 mg) in weekly increments of 5 mg. In the 20 mg group, a dose reduction to 10 mg was permitted when adverse drug reactions occurred at any time after the administration and persisted.

The study included outpatients aged ≥50 years who met the inclusion criteria such as the following:

(a) patients meeting both the diagnostic criteria for AD according to the American Psychiatric Association's Diagnostic and Statistical Manual Version 4 (DSM-IV) and the diagnostic criteria for probable Alzheimer's disease according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA);

(b) patients with a diagnosis of AD confirmed by computerized tomography (CT) or magnetic resonance imaging (MRI) brain scan performed during the 12 months before informed consent or during the run-in period;

(c) patients with a Mini-Mental State Examination (MMSE) score of 3 to 14 (inclusive) and also at Stage ≥6a according to the Functional Assessment Staging (FAST) at 4 weeks before baseline and at baseline; and

(d) patients who had a caregiver who:
    (i) was cooperative and reliable,
    (ii) was able to spend ≥2 days with the patient every week and undertake the protocol-specified observation in terms of activities of daily living, and

(iii) was able to accompany the patient at every clinical evaluation visit.

Concomitant use of donepezil was prohibited, and rehabilitation programs such as an outpatient care program were kept unchanged for 3 months before the start of treatment and throughout the study period.

All of the 51 treated subjects (24 and 27 subjects in the 10 mg and 20 mg groups, respectively) were included in the safety analysis population and the intent-to-treat (ITT) population. Three subjects (1 and 2 subjects, respectively) were withdrawn from the study, and the reasons were adverse events (1 and 2 subjects, respectively) and consent withdrawal (0 and 1 subject, respectively).

The primary endpoints were: CIBIC plus-J, the Alzheimer's Disease Co-operative Study-Activities of Daily Living Inventory, Japanese version (ADCS ADL-J), and SIB-J. Missing data at Week 12 were imputed using the last observation carried forward (LOCF) method.

In the ITT population, the CIBIC plus-J score at Week 12 was "slightly improved" or better in 42% (10 of 24 subjects) in the 10 mg group and 56% (15 of 27 subjects) in the 20 mg group. The change in the ADCS ADL-J score from baseline to Week 12 in the ITT population was 0.79 ± 3.61 (mean ± SD) in the 10 mg group and 0.22 ± 5.32 in the 20 mg group.

The change in the SIB-J score from baseline to Week 12 in the ITT population was 0.58 ± 14.49 in the 10 mg group and 2.89 ± 10.74 in the 20 mg group.

The incidence of adverse events was 37.5% (9 of 24 subjects) in the 10 mg group and 66.7% (18 of 27 subjects) in the 20 mg group. The adverse events reported in ≥2 subjects in either group were constipation (0 and 6 subjects in the 10 mg and 20 mg groups, respectively), dizziness (0 and 4 subjects, respectively), fall (2 and 2 subjects, respectively), diarrhoea NOS (0 and 3 subjects, respectively), pyrexia (0 and 3 subjects, respectively), blood creatine phosphokinase increased (1 and 2 subjects, respectively), blood alkaline phosphatase NOS increased (2 subjects and 1 subject, respectively), and headache NOS (0 and 2 subjects, respectively).

Serious adverse events occurred in 2 subjects in the 10 mg group (haemorrhagic stroke, back pain) and 2 subjects in the 20 mg group (pneumonia NOS, and dehydration/hyperglycaemia NOS), but a causal relationship to the study drug was ruled out for all events. No deaths were reported.

The only non-serious adverse event leading to study drug discontinuation was headache reported in 1 subject in the 20 mg group.

There were no clinically relevant findings in vital signs or laboratory test results. Eight subjects (4 subjects each in the 10 mg and 20 mg groups) underwent ophthalmologic examination, which showed no changes from baseline in lenticular or corneal findings.

4.(iii).A.(4).2) Clinical pharmacology study in patients with AD (5.3.3.2.1, Study IE2201; Studied period, [redacted] 20[redacted] to [redacted] 20[redacted])

The pharmacokinetics, efficacy, and safety of multiple oral doses of memantine in patients with AD were investigated at 7 centers in Japan in a randomized, double-blind, parallel-group, comparative study enrolling Japanese patients with AD (target sample size of 30 subjects, 10 subjects in each group). Subjects received multiple oral doses of memantine at 10 or 20 mg or placebo.

Memantine was administered once daily after breakfast (if missed, the dose was taken no later than 14:00 on the same day). During a double-blind phase (24 weeks), subjects in the memantine group received a dose titrated from 5 mg to the maintenance dose (10 or 20 mg) in weekly increments of 5 mg.

The patients included in the study were those who were outpatients aged ≥50 years and who met the inclusion criteria such as the following:

(a) patients meeting both the diagnostic criteria for AD according to the DSM-IV and the diagnostic criteria for probable Alzheimer's disease according to the NINCDS-ADRDA;
(b) patients with a diagnosis of AD confirmed by CT or MRI brain scan performed during the 12 months before informed consent or during the run-in period;
(c) patients with an MMSE score of ≥10 to ≤20 at the first visit;
(c) patients with a cooperative caregiver who was able to reliably manage the study drug and concomitant medications and who performs other relevant activities for the patients.

In patients who had received donepezil at a constant dose during the 6 months before the start of study treatment, concomitant use of donepezil was permitted provided that the same dosage was maintained as long as possible during the study period. No substantial changes were allowed in rehabilitation programs such as an outpatient care program for 3 months before the start of treatment and throughout the study period (no changes were permitted during the 3 weeks before the evaluation).

All of the 35 treated subjects (12, 11, and 12 subjects in the placebo group, memantine 10 mg group, and memantine 20 mg group, respectively) were included in the safety analysis population and the full analysis set (FAS). Three subjects (1, 0, and 2 subjects, respectively) were withdrawn from the study, with the reasons being adverse events (1, 0, and 1 subjects, respectively) and consent withdrawal (0, 0, and 1 subject, respectively).

In the FAS, the change in the total score of the Alzheimer's Disease Assessment Scale-Japan Cognitive Subscale (ADAS-J cog) from baseline to Week 24 or at the time of withdrawal (LOCF) was 3.16 ± 6.90 (mean ± SD) in the placebo group, 0.93 ± 6.61 in the memantine 10 mg group, and −0.60 ± 4.81 in the memantine 20 mg group.

The incidence of adverse events was 91.7% (11 of 12 subjects) in the placebo group, 72.7% (8 of 11 subjects) in the memantine 10 mg group, and 91.7% (11 of 12 subjects) in the memantine 20 mg group. The adverse events reported in ≥2 subjects in any group were upper respiratory tract inflammation (8.3%

[1 of 12 subjects] in the placebo group, 18.2% [2 of 11 subjects] in the memantine 10 mg group, and 25.0% [3 of 12 subjects] in the memantine 20 mg group), fall (0% [0 of 12 subjects], 9.1% [1 of 11 subjects], and 25.0% [3 of 12 subjects], respectively), pyrexia (0% [0 of 12 subjects], 0% [0 of 11 subjects], and 16.7% [2 of 12 subjects], respectively), blood cholesterol increased (0% [0 of 12 subjects], 0% [0 of 11 subjects], and 16.7% [2 of 12 subjects], respectively), blood creatine phosphokinase increased (8.3% [1 of 12 subjects], 18.2% [2 of 11 subjects], and 8.3% [1 of 12 subjects], respectively), blood pressure increased (0% [0 of 12 subjects], 18.2% [2 of 11 subjects], and 8.3% [1 of 12 subjects], respectively), and memory impairment (16.7% [2 of 12 subjects], 0% [0 of 11 subjects], and 0% [0 of 12 subjects], respectively).

Two serious adverse events (haemoptysis and pyelonephritis) occurred in 2 subjects in the memantine 10 mg group, but a causal relationship to the study drug was ruled out for both events, and both were confirmed to have resolved. No deaths were reported.

The only non-serious adverse event leading to study drug discontinuation was uveitis reported in 1 subject in the memantine 20 mg group.

There were no clinically relevant findings in laboratory test results, vital signs, or ECG.

Abnormal changes from baseline found by ophthalmologic examination were cataract in 1 subject in the placebo group and keratitis in 1 subject in the memantine 20 mg group. Cataract which had been found in 1 subject in the memantine 20 mg group during the run-in period was considered exacerbated after study treatment.

4.(iii).A.(4).3) Late phase II study (5.3.5.1.1; Study IE2101 [double-blind phase]; Studied period, [redacted] 20[redacted] to [redacted] 20[redacted])

A randomized, double-blind, parallel-group, comparative study was conducted in Japanese patients with AD at 53 centers in Japan to investigate the efficacy and safety of memantine in patients with severe AD and to determine the recommended dose for this patient population (target sample size of 300 subjects, 100 subjects in each group). Subjects received oral doses of memantine at 10 or 20 mg or placebo. The development of memantine in Japan originally envisaged the use of data from foreign studies through the adoption of a bridging strategy, and accordingly, this study was designed as a bridging study to extrapolate data from Study MRZ90001-9605 (double-blind phase) [see "4.(iii).A.(7).1) Phase III study in patients with moderately severe to severe AD"], and similarities in the efficacy and safety of memantine were investigated between patients with severe AD in and outside Japan.

Subjects received the study drug once daily after breakfast (if missed, the dose was taken no later than 14:00 on the same day). Placebo was administered during a 4-week run-in period. In the subsequent 24-week double-blind phase, subjects in the memantine groups received memantine at a dose titrated from

5 mg to the maintenance dose (10 or 20 mg) in weekly increments of 5 mg.

The main inclusion criteria were the same as those in the early phase II study (Study IE2901) except for the following: patients with an MMSE score of ≥5 to ≤14 and also at a FAST stage of ≥6a to ≤7a before the start of both the run-in period and the double-blind phase. Concomitant use of donepezil was prohibited. No substantial changes were allowed in rehabilitation programs such as an outpatient care or rehabilitation service program for 3 months before the start of the double-blind phase and throughout the study period (no changes were permitted during the 3 weeks before the evaluation). A temporary short-stay was permitted unless it overlapped with the 3-week period before efficacy evaluation.

All of the 315 treated subjects (108, 107, and 100 subjects in the placebo, memantine 10 mg, and memantine 20 mg groups, respectively) were included in the safety analysis population, and 314 subjects, excluding 1 subject in the placebo group who was diagnosed as having Creutzfeldt-Jakob disease (a type of dementia distinct from AD), were included in the FAS, which was defined as the primary efficacy analysis population. Of the subjects included in the safety analysis population, 51 subjects (21, 14, and 16 subjects, respectively) were withdrawn from the study, with the main reason being adverse events (15, 6, and 8 subjects, respectively). The primary endpoints were ADCS ADL-J and SIB-J scores. Primary efficacy analysis was performed by the observed case (OC) approach without imputing missing data, using the data from only those subjects for whom efficacy had been evaluated at the specified assessment time points.

The changes over time in the ADSC ADL-J score (one of the primary endpoints) from baseline to each time point are shown in Figure 1. The ADCS ADL-J score at baseline was 31.59 ± 10.12 (mean ± SD) in the placebo group (107 subjects), 30.24 ± 10.76 in the memantine 10 mg group (107 subjects), and 32.81 ± 9.70 in the memantine 20 mg group (100 subjects). The change in the ADCS ADL-J score at Week 24 was −2.19 ± 5.37 (mean ± SD) in the placebo group (85 subjects), −1.48 ± 5.32 in the memantine 10 mg group (92 subjects), and −1.63 ± 6.13 in the memantine 20 mg group (83 subjects). The changes in the ADCS ADL-J score up to Week 24 showed no significant dose response when examined using a one-way analysis of variance model with contrast coefficients of [−1, 0, 1] assigned to the placebo, memantine 10 mg, and memantine 20 mg groups, respectively (P = 0.5168). No significant difference was detected in the changes in the ADCS-ADL-J score at Week 24 by pair-wise comparison among the 3 groups (placebo group vs. memantine 10 mg group, P = 0.5267; placebo group vs. memantine 20 mg group, P = 0.8975; memantine 10 mg group vs. the memantine 20 mg group, P = 0.5702; Wilcoxon test).

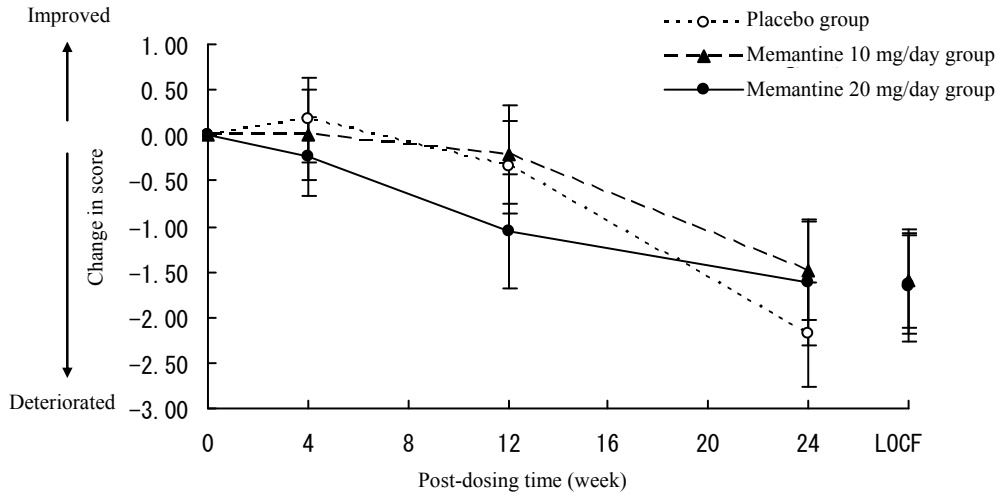


Figure 1. Changes in the ADCS ADL-J score over time (FAS [OC and LOCF]) (mean ± standard error)

The changes over time in the SIB-J score (the other primary endpoint) from baseline to each time point are shown in Figure 2. The SIB-J score at baseline was 72.57 ± 17.84 (mean ± SD) in the placebo group (107 subjects), 69.06 ± 17.77 in the memantine 10 mg group (107 subjects), and 71.78 ± 17.89 in the memantine 20 mg group (100 subjects), and the change in the SIB-J score at Week 24 was −3.71 ± 10.01 (mean ± SD) in the placebo group (85 subjects), −2.85 ± 9.09 in the memantine 10 mg group (92 subjects), and 0.39 ± 6.56 in the memantine 20 mg group (83 subjects). The changes in the SIB-J score at Week 24 showed a significant dose response when examined using a one-way analysis of variance model with contrast coefficients of [−1, 0, 1] assigned to the placebo, memantine 10 mg, and memantine 20 mg groups, respectively ($P = 0.0026$). In terms of the changes in the SIB-J score up to Week 24, no significant difference was detected by pair-wise comparison between the placebo group and the memantine 10 mg group ($P = 0.4173$, Wilcoxon test), but significant differences were detected between the placebo group and the memantine 20 mg group and between the memantine 10 mg group and the 20 mg group ($P = 0.0029$ and 0.0217, respectively; Wilcoxon test).

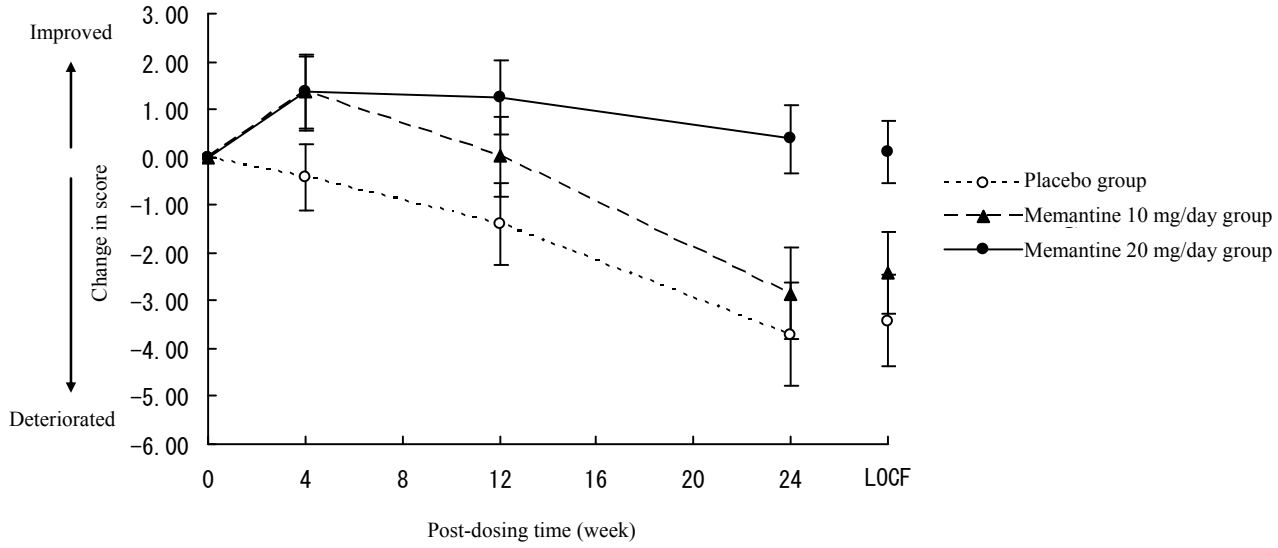


Figure 2. Changes in the SIB-J score over time (FAS [OC and LOCF]) (mean ± standard error)

The changes in the CIBIC plus-J score (one of the secondary endpoints) over time are shown in Figure 3 (calculated based on a 7-point scale from "markedly improved" to "markedly worse" [point 1-7]). The CIBIC plus-J score at Week 24 was 4.69 ± 1.31 (mean ± SD) in the placebo group (85 subjects), 4.55 ± 1.49 in the memantine 10 mg group (92 subjects), and 4.36 ± 1.64 in the memantine 20 mg group (83 subjects). The changes in the CIBIC plus-J score at Week 24 showed no significant dose response when examined using a one-way analysis of variance model with contrast coefficients of [−1, 0, 1] assigned to the placebo, memantine 10 mg, and memantine 20 mg groups, respectively ($P = 0.1482$). No dose response was detected in the frequency distribution of the CIBIC plus-J scores at Week 24 weeks by pair-wise comparison among the 3 groups ($P = 0.1474$; Mantel test). No significant difference was detected in the CIBIC plus-J scores at Week 24 by pair-wise comparison among the 3 groups (placebo group vs. memantine 10 mg group, $P = 0.4924$; placebo group vs. memantine 20 mg group, $P = 0.2503$; memantine 10 mg group vs. the memantine 20 mg group, $P = 0.5812$; Wilcoxon test).

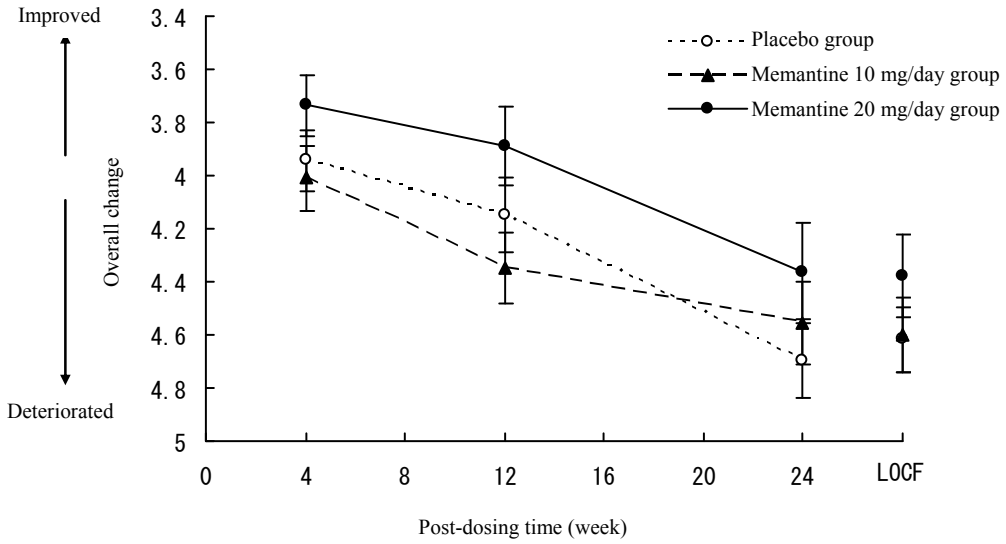


Figure 3. Changes in the CIBIC plus-J score over time (FAS [OC and LOCF]) (mean ± standard error)

Although conducted as a bridging study, this study was considered to have failed to meet the requirements for serving as a bridging study because of the lack of a significant difference in the ADCS ADL-J score, one of the primary endpoints, between the memantine 20 mg group and the placebo group.

The incidence of adverse events was 72.2% (78 of 108 subjects) in the placebo group, 77.6% (83 of 107 subjects) in the memantine 10 mg group, and 72.0% (72 of 100 subjects) in the memantine 20 mg group. The adverse events reported in ≥5% of subjects in any group are shown in Table 1.

Table 1. Adverse events reported in ≥5% of subjects in any group

	Placebo group N = 108	Memantine 10 mg group N = 107	Memantine 20 mg group N = 100
Overall incidence	72.2 (78)	77.6 (83)	72.0 (72)
Nasopharyngitis	11.1 (12)	18.7 (20)	14.0 (14)
Contusion	5.6 (6)	1.9 (2)	10.0 (10)
Constipation	9.3 (10)	11.2 (12)	7.0 (7)
Fall	7.4 (8)	4.7 (5)	6.0 (6)
Upper respiratory tract inflammation	4.6 (5)	3.7 (4)	6.0 (6)
Insomnia	4.6 (5)	3.7 (4)	5.0 (5)
Back pain	0.9 (1)	1.9 (2)	5.0 (5)
Oedema peripheral	6.5 (7)	9.3 (10)	4.0 (4)
Faecal incontinence	1.9 (2)	7.5 (8)	3.0 (3)
Weight decreased	3.7 (4)	5.6 (6)	2.0 (2)
Urinary incontinence	2.8 (3)	7.5 (8)	1.0 (1)
Blood creatine phosphokinase increased	5.6 (6)	1.9 (2)	1.0 (1)

% (number of subjects)

One subject in the memantine 10 mg group died (head injury) and 1 subject in the placebo group died (pneumonia). The death in the memantine 10 mg group (head injury) was assessed as unrelated to the study drug. The death in the placebo group (pneumonia) was considered to be an incidental event in

consideration of the time course from the start of study treatment to its onset. However, its causal relationship to the study drug was assessed as unknown because the details were unknown. The incidence of serious adverse events was 10.2% (11 of 108 subjects) in the placebo group, 9.3% (10 of 107 subjects) in the memantine 10 mg group, and 7.0% (7 of 100 subjects) in the memantine 20 mg group. A causal relationship to the study drug was not ruled out for the following serious non-fatal adverse events: hepatic function abnormal, urinary retention/ileus, and vomiting/diarrhoea in 3 subjects in the placebo group; urinary tract infection and reflux oesophagitis/oesophageal ulcer/anaemia in 2 subjects in the memantine 10 mg group; and femur fracture and urinary retention/urinary tract infection/postrenal failure/dehydration in 2 subjects in the memantine 20 mg group.

Non-serious adverse events led to study drug discontinuation in 5 subjects in the placebo group, 1 subject in the memantine 10 mg group, and 4 subjects in the memantine 20 mg group. A causal relationship to the study drug was not ruled out for the following adverse events: delusion/restlessness, excitability, anxiety, arthralgia/pain in extremity, and atrial fibrillation in 5 subjects in the placebo group; and inappetence/dehydration, decreased activity/decreased appetite, malaise/gait abnormal/nausea, and delusion/excitability in 4 subjects in the memantine 20 mg group.

Ophthalmologic examination (lens and cornea) was performed in 38, 28, and 34 subjects in the placebo, memantine 10 mg, and memantine 20 mg groups, respectively, and the following subjects were assessed to “have no abnormalities” at baseline and “have abnormalities” at the final evaluation: 2 subjects (lenticular and corneal abnormalities) in the placebo group, 1 subject (lenticular abnormality) in the memantine 10 mg group, and 0 subjects in the memantine 20 mg group.

4.(iii).A.(5) Japanese phase III studies

4.(iii).A.(5).1) Phase III study in patients with severe AD (5.3.5.1.2; Study IE3501; Studied period, [redacted] 20[redacted] to [redacted] 20[redacted])

The efficacy of memantine in patients with severe AD was verified and its safety was investigated at 74 centers in Japan in a randomized, double-blind, parallel-group, comparative study enrolling Japanese patients with AD (target sample size of 400 subjects, 200 subjects in each group). Subjects received oral doses of memantine at 20 mg or placebo.

The study drug was administered once daily after breakfast (if missed, the dose was taken before evening meal on the same day). Placebo was administered in the 4-week run-in period. In the subsequent 24-week double-blind phase, subjects in the memantine group received memantine at a dose titrated from 5 mg to 20 mg in weekly increments of 5 mg.

The main inclusion criteria were generally the same as those in the late phase II study (Study IE2101 [double-blind phase]) except for the following:

(a) patients with a diagnosis of AD confirmed by CT or MRI brain scan performed during the period from 6 months before informed consent to the day of second-stage registration;

(b) patients for whom throughout the study period the same caregiver:
    (i) was able to undertake an adequate observation of activities of daily living (during a daytime stay on ≥3 days every week), and
    (ii) was able to accompany at every efficacy evaluation visit.

Concomitant use of donepezil was prohibited. Ongoing rehabilitation programs, such as an outpatient care or rehabilitation service program, which had been started before the run-in period were continued throughout the study period without any change in contents or frequency. Use of a short-stay program was restricted to a maximum of 6 overnight stays during each interval between scheduled visits, and was prohibited during the 3 weeks before efficacy evaluation both in the run-in period and during the 3 weeks before efficacy evaluation conducted after 24 weeks of the double-blind phase.

All of the 432 subjects treated in the double-blind phase (211 and 221 subjects in the placebo and memantine 20 mg groups, respectively) were included in the safety analysis population, and 426 subjects (208 and 218 subjects, respectively) were included in the FAS, which was defined as the primary efficacy analysis population, with the exclusion of 6 subjects (3 and 3 subjects, respectively) for whom both of the primary endpoints, SIB-J and Modified CIBIC plus-J (CIBIC plus-J with one of its subscales, "disability assessment for dementia [DAD]," replaced by FAST[*]), had not been evaluated after the start of the double-blind phase (or those whose data were obtained but rejected). Of subjects included in the safety analysis population, 62 subjects (33 and 29 subjects, respectively) were withdrawn from the study, with the main reasons (multiple reasons allowed) being request for withdrawal (17 and 14 subjects, respectively) and adverse events (13 and 14 subjects, respectively). Primary efficacy analysis was performed by the OC method.

The changes over time in the SIB-J score (one of the primary endpoints) from baseline to each time point are shown in Figure 4. The SIB-J score at baseline was 70.05 ± 18.66 (mean ± SD) in the placebo group (206 subjects) and 71.90 ± 17.12 in the memantine 20 mg group (218 subjects), and the change in the SIB-J score at Week 24 was −5.18 ± 11.66 in the placebo group (175 subjects) and −0.65 ± 9.74 in the memantine 20 mg group (193 subjects) with a significant difference shown between the groups, and the superiority of the memantine 20 mg group over the placebo group (P = 0.0001, Wilcoxon test) was demonstrated.

[*] The results of Study IE2101 (double-blind phase) suggested that the use of DAD, a subscale of CIBIC plus-J, was unsuitable for evaluation of patients with severe AD because many of its assessment variables, such as cooking, making phone calls, monetary transactions, and communication, are not undertaken by this patient population on a daily basis.

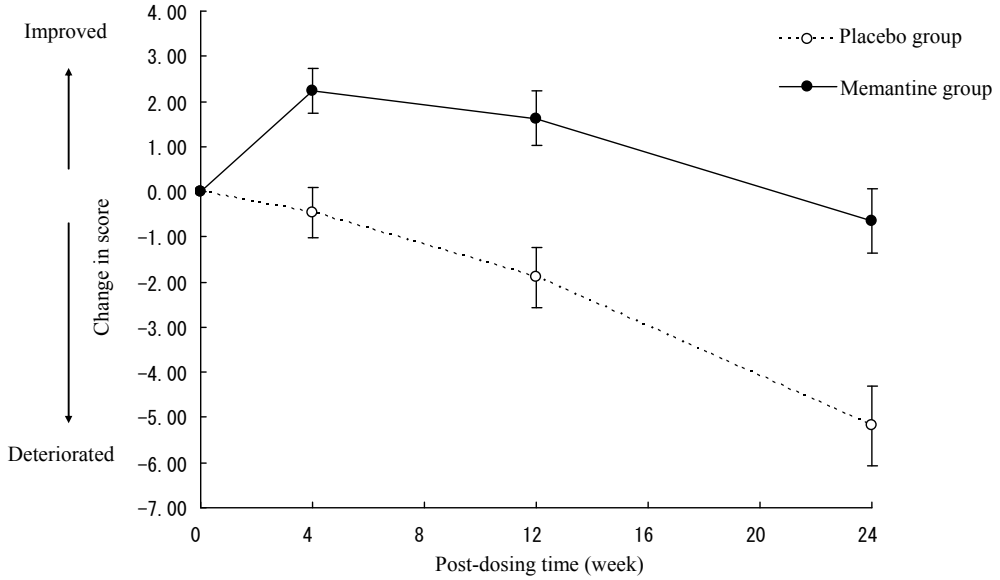


Figure 4. Changes in the SIB-J score over time (FAS [OC]) (mean ± standard error)

The changes in the Modified CIBIC plus-J score (the other primary endpoint) over time are shown in Figure 5. The Modified CIBIC plus-J score at Week 24 was 4.58 ± 1.01 (mean ± SD) in the placebo group (177 subjects) and 4.47 ± 1.07 in the memantine 20 mg group (190 subjects), with no significant difference shown between the groups (P = 0.3189, Mantel test).

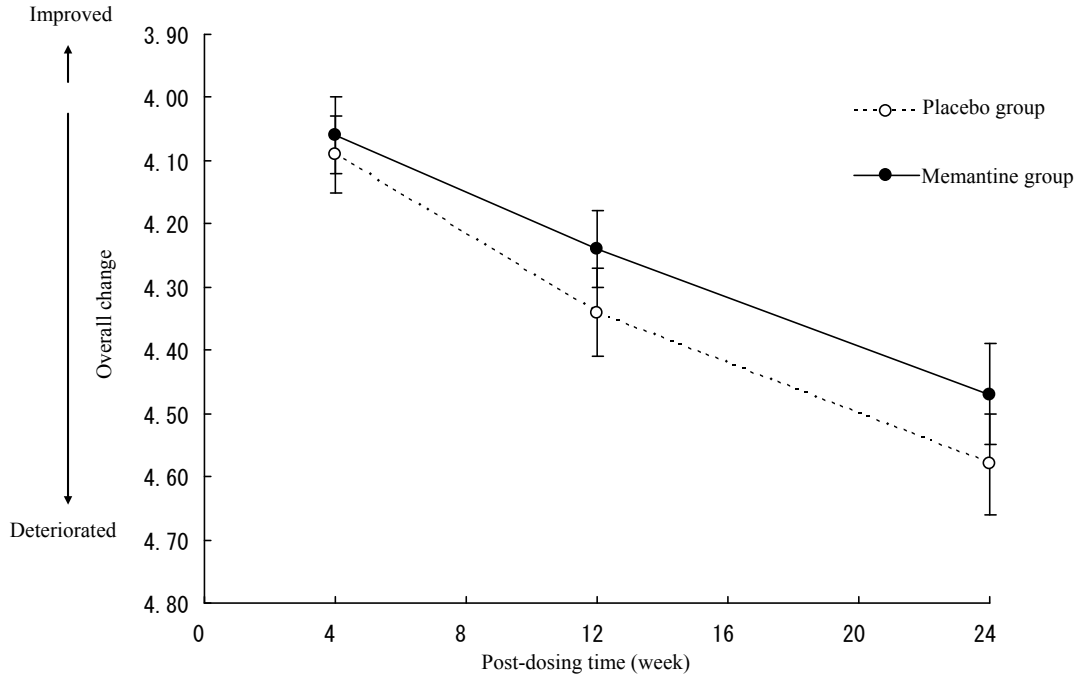


Figure 5. Changes in the Modified CIBIC plus-J score over time (FAS [OC]) (mean ± standard error)

The incidence of adverse events was 79.1% (167 of 211 subjects) in the placebo group and 81.4% (180 of 221 subjects) in the memantine 20 mg group. The adverse events reported in ≥3% of subjects in either group are shown in Table 2.

Table 2. Adverse events reported in ≥3% of subjects in either group

	Placebo group N = 211	Memantine 20 mg group N = 221
Overall incidence	79.1 (167)	81.4 (180)
Nasopharyngitis	19.9 (42)	14.5 (32)
Constipation	10.9 (23)	13.6 (30)
Fall	11.8 (25)	11.3 (25)
Insomnia	5.2 (11)	6.3 (14)
Contusion	8.5 (18)	5.0 (11)
Diarrhoea	6.2 (13)	4.5 (10)
Alzheimer's disease	8.1 (17)	4.1 (9)
Back pain	3.8 (8)	4.1 (9)
Blood pressure increased	2.8 (6)	4.1 (9)
Pollakiuria	1.4 (3)	4.1 (9)
Vomiting	7.6 (16)	3.6 (8)
Pyrexia	3.3 (7)	3.6 (8)
Weight decreased	2.8 (6)	3.2 (7)
Dizziness	1.4 (3)	3.2 (7)
Hypertension	0.9 (2)	3.2 (7)
Restlessness	3.3 (7)	2.3 (5)
Excoriation	3.8 (8)	1.8 (4)
Blood creatine phosphokinase increased	3.3 (7)	1.8 (4)
Oedema peripheral	3.3 (7)	1.4 (3)

% (number of subjects)

Two subjects in the placebo group died (pneumonia/multi-organ failure/disseminated intravascular coagulation, and drowning) and 5 subjects in the memantine 20 mg group died (prostate cancer, colon cancer/pneumonia/sepsis[*]/disseminated intravascular coagulation,[*] pancreatitis acute, aortic aneurysm rupture, and fungal infection). Except for the pancreatitis acute in 1 subject in the memantine 20 mg group, all of these events were assessed as unrelated to the study drug. Although pancreatitis acute may have been an incidental event, given that this event occurred on Day 27, its causal relationship to the study drug could not be ruled out, and was therefore assessed as unknown. The incidence of serious adverse events was 11.4% (24 of 211 subjects) in the placebo group and 11.8% (26 of 221 subjects) in the memantine 20 mg group. A causal relationship to the study drug was not ruled out for the following serious non-fatal adverse events: hypoglycaemia/syncope, bladder cancer, and neurogenic bladder in 3 subjects in the placebo group and pneumonia/blood creatine phosphokinase increased, memory impairment/delusion/agitation, hyperammonaemia, Alzheimer's disease, hepatic function abnormal, cholecystitis acute, cerebral infarction, cardiac failure acute, and convulsion in 9 subjects in the memantine 20 mg group.

The incidence of non-serious adverse events leading to study drug discontinuation was 3.8% (8 of 211 subjects) in the placebo group and 2.3% (5 of 221 subjects) in the memantine 20 mg group. Among these adverse events, a causal relationship to the study drug was not ruled out for the following events that occurred during the double-blind phase: Alzheimer's disease in 3 subjects and restlessness in 1 subject in the placebo group, and agitation and dizziness in 2 subjects in the memantine 20 mg group.

Ophthalmologic examination (lens, cornea) was performed in 87 and 98 subjects in the placebo and

[*] Not included in the summary of adverse events because these events occurred after the end of follow-up period.

memantine 20 mg groups, respectively, and the following subjects were assessed to “have no abnormalities” at baseline and “have abnormalities” at the final evaluation: 1 subject (corneal abnormality) in the placebo group and 1 subject (lenticular abnormality) in the memantine 20 mg group.

4.(iii).A.(5).2) Study on compliance with 20 mg tablets (5.3.5.4.1; Study IE3604; Studied period, [redacted] 20[redacted] to [redacted] 20[redacted])

Compliance with and the safety of once-daily oral administration of memantine 20 mg tablets after breakfast were investigated at 10 centers in Japan in an open-label study enrolling Japanese patients who had completed Study IE3501 (target sample size of 20 subjects).

Memantine was administered once daily after breakfast (if missed, the dose was taken no later than start time of dinner on the same day) for 12 weeks. The dose was titrated from 5 mg to 20 mg as the maintenance dose in weekly increments of 5 mg.

The main inclusion criterion was completion of Study IE3501. Concomitant use of donepezil was permitted provided that the same dosage had been maintained during the 1 month before baseline, and was also maintained throughout the study period.

This study enrolled 21 patients out of those who had completed Study IE3501. All of the 21 subjects received the study drug, and were assessed for safety and efficacy. One subject was withdrawn from the study due to an adverse event.

The compliance rate ([(Treatment period – Number of noncompliant days during treatment period)/Treatment period] × 100), the primary endpoint, was 97.98% ± 4.71% (mean ± SD).

The incidence of adverse events was 61.9% (13 of 21 subjects), and the adverse events reported in ≥2 subjects were insomnia (14.3% [3 of 21 subjects]), and constipation, nausea, vomiting, nasopharyngitis, fall, and headache (9.5% [2 of 21 subjects] for each event).

No deaths were reported. The serious adverse events were loss of consciousness and subdural haematoma reported in 1 subject each, but a causal relationship to the study drug was ruled out for these events.

Non-serious adverse events led to study drug discontinuation in 1 subject (dizziness/inappetence/anxiety). These events were assessed as related to the study drug, but were not attributed to the shape of the 20 mg tablet.

There were no clinically relevant changes in laboratory test results.

4.(iii).A.(5).3) Phase III study in patients with mild to moderate AD (5.3.5.1.3; Study MA3301; Studied period, [redacted] 20[redacted] to [redacted] 20[redacted])

The dose-response relationship and efficacy of memantine in patients with mild to moderate AD were verified and its safety was investigated at 63 centers in Japan in a randomized, double-blind, parallel-group, comparative study enrolling Japanese patients with AD. Subjects received oral doses of memantine at 10 or 20 mg or placebo. The target sample size was originally 450 subjects (150 subjects in each group), which was modified to 540 (180 subjects in each group) on [redacted], 20[redacted] in consideration of the results of a US phase III study in patients with mild to moderate AD (Study MEM-MD-10) published while Study MA3301 was underway.

Subjects received the study drug once daily after breakfast (if missed, the dose was taken no later than start time of evening meal on the same day). Placebo was administered during the 4-week run-in period. In the subsequent 24-week double-blind phase, subjects in the memantine group received memantine at a dose titrated from 5 mg to the maintenance dose (10 or 20 mg) in weekly increments of 5 mg.

The patients included in the study were those who were outpatients aged ≥50 years and who met the inclusion criteria such as the following:

(a) patients meeting the diagnostic criteria for probable Alzheimer's disease according to the NINCDS-ADRDA;
(b) patients with an MMSE score of ≥10 to ≤23;
(c) patients who had a caregiver living with them or within a visiting distance, and who were able to be accompanied by the same caregiver at every clinical evaluation visit throughout the study period.

Concomitant use of donepezil was prohibited. Rehabilitation programs that had been started before the run-in period were continued until the 10th visit (4 weeks after the final dose in the double-blind phase) without any change in contents or frequency. No new rehabilitation programs were allowed to be started during the period from the start of the run-in period until the 10th visit (4 weeks after the final dose in the double-blind phase).

A total of 564 subjects (186, 190, and 188 subjects in the placebo, memantine 10 mg, and memantine 20 mg groups, respectively) enrolled in the double-blind phase were included in the safety analysis population, with the exclusion of 1 subject who did not receive any study drug (10 mg group), and 557 subjects (180, 190, and 187 subjects, respectively) were included in the FAS, which was defined as the primary efficacy analysis population, with the exclusion of 7 subjects who had not been evaluated for ADAS-J cog or CIBIC-plus scores after the start of the double-blind phase. Of the safety analysis population, 64 subjects (26, 12, and 26 subjects, respectively) were withdrawn from the study, with the main reasons (multiple reasons allowed) being adverse events (10, 6, and 16 subjects, respectively) and request for withdrawal (14, 5, and 9 subjects, respectively). Primary efficacy analysis was performed by the LOCF method.

The change in the ADAS-J cog score (one of the primary endpoints) from baseline to Week 24 was 1.82

± 4.72 (mean ± SD) in the placebo group, 0.57 ± 4.54 in the memantine 10 mg group, and 1.41 ± 4.50 in the memantine 20 mg group, with no significant dose-response relationship shown by a contrast test using the maximum contrast method with contrast coefficients of [−1, 0, 1] and [−2, 1, 1].

The CIBIC-plus score (the other primary endpoint) at Week 24 was 4.53 ± 1.04 (mean ± SD) in the placebo group, 4.30 ± 1.08 in the memantine 10 mg group, and 4.28 ± 0.99 in the memantine 20 mg group. A contrast test using the maximum contrast method with contrast coefficients of [−1, 0, 1] and [−2, 1, 1] detected a significant dose-response relationship with contrast coefficients of [−2, 1, 1] (P = 0.0197; a one-sided significance level of 2.5%).

The incidence of adverse events was 76.9% (143 of 186 subjects) in the placebo group, 75.8% (144 of 190 subjects) in the memantine 10 mg group, and 79.8% (150 of 188 subjects) in the memantine 20 mg group. The adverse events reported in ≥3% of subjects in any group are shown in Table 3.

Table 3. Adverse events reported in ≥3% of subjects in any group

	Placebo group N = 186	Memantine 10 mg group N = 190	Memantine 20 mg group N = 188
Overall incidence	76.9 (143)	75.8 (144)	79.8 (150)
Nasopharyngitis	15.1 (28)	18.4 (35)	16.5 (31)
Dizziness	2.7 (5)	2.1 (4)	10.1 (19)
Constipation	4.3 (8)	6.3 (12)	8.0 (15)
Fall	7.5 (14)	5.3 (10)	8.0 (15)
Headache	4.3 (8)	4.7 (9)	6.9 (13)
Blood creatine phosphokinase increased	3.8 (7)	4.2 (8)	6.9 (13)
Contusion	3.2 (6)	3.2 (6)	5.9 (11)
Blood urine present	3.8 (7)	1.6 (3)	5.3 (10)
Diarrhoea	7.0 (13)	3.2 (6)	4.8 (9)
Back pain	2.7 (5)	3.7 (7)	4.3 (8)
White blood cell count increased	2.7 (5)	2.6 (5)	4.3 (8)
Blood alkaline phosphatase increased	3.8 (7)	1.1 (2)	4.3 (8)
Blood triglycerides increased	2.7 (5)	3.7 (7)	3.7 (7)
Glucose urine present	1.6 (3)	2.6 (5)	3.7 (7)
Arthralgia	1.1 (2)	2.6 (5)	3.7 (7)
Weight decreased	3.8 (7)	1.6 (3)	3.7 (7)
Blood glucose increased	2.2 (4)	1.6 (3)	3.7 (7)
Protein urine present	1.6 (3)	1.1 (2)	3.7 (7)
Eczema	2.2 (4)	1.6 (3)	3.2 (6)
Alanine aminotransferase increased	1.1 (2)	1.1 (2)	3.2 (6)
Blood urea increased	0.5 (1)	1.1 (2)	3.2 (6)
Inappetence	0.5 (1)	1.1 (2)	3.2 (6)
Vomiting	2.2 (4)	5.3 (10)	2.7 (5)
Hypertension	0.5 (1)	3.2 (6)	2.7 (5)

% (number of subjects)

One subject in the memantine 10 mg group died (cerebral haemorrhage/pneumonia aspiration/staphylococcal infection) and 1 subject in the memantine 20 mg group died (abnormal behavior/death), and all of the adverse events observed in these subjects were assessed as unrelated to the study drug. The incidence of serious adverse events was 5.9% (11 of 186 subjects) in the placebo group, 2.6% (5 of 190 subjects) in the memantine 10 mg group, and 7.4% (14 of 188 subjects) in the

memantine 20 mg group. A causal relationship to the study drug was not ruled out for the following serious non-fatal adverse events: gastric ulcer, pneumonia, and hepatic function abnormal in 3 subjects in the placebo group, cardiac failure congestive/atrial fibrillation and meningoencephalitis bacterial in 2 subjects in the memantine 10 mg group, and inappetence/weight decreased (2 subjects), large intestinal haemorrhage, femur fracture, glaucoma/retinal vein occlusion, convulsion, and depressed level of consciousness/blood pressure decreased (1 subject each) reported in a total of 7 subjects in the memantine 20 mg group.

The incidence of non-serious adverse events leading to study drug discontinuation was 2.7% (5 of 186 subjects) in the placebo group, 1.6% (3 of 190 subjects) in the memantine 10 mg group, and 4.8% (9 of 188 subjects) in the memantine 20 mg group. Among these adverse events, a causal relationship to the study drug was not ruled out for the following events that had occurred during the double-blind phase: mood variable/insomnia/paraesthesia oral, drug eruption, affect lability/illusion/hallucination auditory, and anaemia in 4 subjects in the placebo group, eczema nummular, toxic skin eruption, and anxiety disorder in 3 subjects in the memantine 10 mg group, and dizziness (3 subjects), headache/dizziness/somnolence, hallucination/delusion, decreased appetite, autonomic nervous system imbalance, and spinal osteoarthritis/cervical spinal stenosis (1 subject each) in a total of 8 subjects in the memantine 20 mg group.

Ophthalmologic examination (lens, cornea) was performed in 103, 108, and 105 subjects in the placebo, memantine 10 mg, and memantine 20 mg groups, respectively, and the following subjects were assessed as “normal” or “abnormal (not clinically relevant)” at baseline and as “abnormal (clinically relevant)” at the final evaluation: 8 subjects (lenticular and corneal abnormalities in 3 and 5 subjects, respectively) in the placebo group, 3 subjects (2 and 1 subjects, respectively) in the memantine 10 mg group, and 5 subjects (1 and 5 subjects, respectively) in the memantine 20 mg group.

4.(iii).A.(6) Japanese long-term studies

4.(iii).A.(6).1) Long-term extension study of Study IE2101 (double-blind phase) (1) (5.3.5.2.2; Study IE2101 [open-label extension phase]; Studied period, [redacted] 20[redacted] to [redacted] 20[redacted])

The long-term safety and efficacy of memantine were investigated at 47 centers in Japan in an open-label study (the open-label extension phase of Study IE2101) enrolling patients who had completed the double-blind phase of Study IE2101.

Memantine was administered for 28 weeks to subjects enrolled in the open-label extension phase after completing the double-blind phase of Study IE2101. Subjects received memantine once daily after breakfast (if missed, the dose was taken no later than 14:00 on the same day) at a daily dose titrated from 5 mg to the maintenance dose (20 mg) in weekly increments of 5 mg. Subjects who had adverse drug reactions possibly attributable to the dose level of memantine during Weeks 3 to 28 in the open-label extension phase were allowed to take the study drug in divided doses after breakfast and lunch (no later than 14:00) or at a dose reduced to 10 mg.

The main inclusion criterion was completion of the double-blind phase of Study IE2101, and the requirements concerning the use of concomitant drugs and rehabilitation programs, such as an outpatient care or rehabilitation service program, were the same as those in the double-blind phase of Study IE2101.

Of the 264 subjects who had completed the double-blind phase of Study IE2101 (87 subjects in the placebo groups, 93 subjects in the memantine 10 mg groups, and 84 subjects in the memantine 20 mg groups, respectively), 245 subjects (81 subjects in the group of placebo → memantine 20 mg [P-H group]; 86 subjects in the group of memantine 10 mg → memantine 20 mg [L-H group]; and 78 subjects in the group of memantine 20 mg → memantine 20 mg [H-H group]) were enrolled in the open-label extension phase, and all of the 245 subjects were included in the safety analysis population and the FAS. A total of 37 subjects (18 subjects in the P-H group, 11 subjects in the L-H group, and 8 subjects in the H-H group) were withdrawn from the study, with the main reason being adverse events (11 subjects in the P-H group, 5 subjects in the L-H group, and 5 subjects in the H-H group). During the open-label extension phase, 4 subjects (2 subjects each in the P-H group and the L-H group) required a dose reduction of memantine.

In an OC analysis of the FAS, changes in the ADCS ADL-J score, one of the primary endpoints, (score at Week 28 in the open-label extension phase – score at baseline in the double-blind phase) were −4.15 ± 6.92 (mean ± SD) for the P-H group (62 subjects), −4.52 ± 8.04 for the L-H group (73 subjects), and −4.56 ± 6.86 for the H-H group (68 subjects).

In an OC analysis of the FAS, changes in the SIB-J score, the other primary endpoint, (score at Week 28 in the open-label extension phase – score at baseline in the double-blind phase) were −7.68 ± 12.84 (mean ± SD) for the P-H group (62 subjects), −9.40 ± 13.58 for the L-H group (72 subjects), and −7.09 ± 10.71 for the H-H group (67 subjects).

The incidence of adverse events reported during the open-label extension phase was 79.0% (64 of 81 subjects) in the P-H group, 77.9% (67 of 86 subjects) in the L-H group, and 76.9% (60 of 78 subjects) in the H-H group. The adverse events reported in ≥3% of subjects in any group are shown in Table 4.

Table 4. Adverse events reported in ≥3% of subjects in any group

	P-H group N = 81	L-H group N = 86	H-H group N = 78
Overall incidence	79.0 (64)	77.9 (67)	76.9 (60)
Nasopharyngitis	18.5 (15)	12.8 (11)	10.3 (8)
Alzheimer's disease	2.5 (2)	11.6 (10)	9.0 (7)
Upper respiratory tract inflammation	1.2 (1)	2.3 (2)	9.0 (7)
Urinary incontinence	1.2 (1)	3.5 (3)	7.7 (6)
Constipation	8.6 (7)	15.1 (13)	6.4 (5)
Fall	7.4 (6)	8.1 (7)	6.4 (5)
Poriomania	3.7 (3)	2.3 (2)	6.4 (5)
Insomnia	6.2 (5)	1.2 (1)	6.4 (5)
Diarrhoea	6.2 (5)	3.5 (3)	5.1 (4)
Anger	1.2 (1)	2.3 (2)	5.1 (4)
Contusion	1.2 (1)	7.0 (6)	3.8 (3)
Faecal incontinence	2.5 (2)	2.3 (2)	3.8 (3)
Blood alkaline phosphatase increased	2.5 (2)	2.3 (2)	3.8 (3)
Pyrexia	1.2 (1)	1.2 (1)	3.8 (3)
Back pain	0 (0)	1.2 (1)	3.8 (3)
Disturbance in attention	0 (0)	1.2 (1)	3.8 (3)
Eczema	2.5 (2)	4.7 (4)	2.6 (2)
Cognitive disorder	1.2 (1)	4.7 (4)	2.6 (2)
Blood glucose increased	4.9 (4)	3.5 (3)	2.6 (2)
Oedema peripheral	2.5 (2)	3.5 (3)	2.6 (2)
Rash	1.2 (1)	3.5 (3)	2.6 (2)
Anxiety	4.9 (4)	2.3 (2)	2.6 (2)
Vomiting	3.7 (3)	2.3 (2)	2.6 (2)
Weight decreased	2.5 (2)	3.5 (3)	1.3 (1)
Gait abnormal	0 (0)	3.5 (3)	1.3 (1)
Excitability	8.6 (7)	1.2 (1)	1.3 (1)
Haemorrhoids	4.9 (4)	1.2 (1)	1.3 (1)
Glucose urine present	3.7 (3)	2.3 (2)	0 (0)

% (number of subjects)

One subject in the L-H group died (rectal cancer), and this death was assessed as unrelated to the study drug. The incidence of serious adverse events was 13.6% (11 of 81 subjects) in the P-H group, 10.5% (9 of 86 subjects) in the L-H group, and 9.0% (7 of 78 subjects) in the H-H group. A causal relationship to the study drug was not ruled out for the following serious non-fatal adverse events: dyspnoea and encephalopathy in 2 subjects in the P-H group, and anxiety/anger/restlessness and insomnia/anger/excitability/aggression in 2 subjects in the H-H group.

Non-serious adverse events led to study drug discontinuation in 7 subjects in the P-H group and 1 subject in the L-H group. A causal relationship to the study drug was not ruled out for the non-serious adverse events reported in 5 subjects in the P-H group (excitability [2 subjects] and hepatic function abnormal, vomiting/dizziness, and aggression/excitability [1 subject each]) and 1 subject in the L-H group (abnormal behaviour).

Ophthalmologic examination (lens, cornea) was performed in 23, 25, and 29 subjects in the P-H, L-H, and H-H groups, respectively, and the following subjects were assessed to "have no abnormalities" before the start of the open-label extension phase and "have abnormalities" at the final evaluation: 1 subject (corneal abnormality) in the P-H group, 2 subjects (lenticular abnormality) in the L-H group,

and 3 subjects (lenticular abnormality, 2; corneal abnormality, 1) in the H-H group.

4.(iii).A.(6).2) Long-term extension study of Studies IE2901, IE2101 (open-label extension phase), and IE2201 (5.3.5.2.4; Study IE2301; Studied period, [redacted] 20[redacted] to [redacted] 20[redacted])

The long-term safety of memantine was investigated at 42 centers in Japan in an open-label study enrolling Japanese patients who had completed Study IE2901, IE2101 (open-label extension phase), or IE2201, and wished to continue treatment.

Subjects received memantine once daily after breakfast (if missed, the dose was taken no later than 14:00 on the same day) at a daily dose titrated from 5 mg to 20 mg in weekly increments of 5 mg. The maintenance dose was 10 mg for subjects who had required a dose reduction to 10 mg due to adverse drug reactions in the previous study. Subjects who had adverse drug reactions that were considered attributable to the dose level at Week 3 or later in this study were allowed to take the study drug at a dose reduced to 10 mg or in 2 divided doses. The mean duration of treatment in this study was 508.1 days.

The main inclusion criterion was completion of Study IE2901, IE2101 (open-label extension phase), or IE2201. Concomitant use of amantadine hydrochloride or any investigational products other than memantine was prohibited.

This study enrolled a total of 189 patients (1 from Study IE2901, 156 from Study IE2101 [open-label extension phase], and 32 from Study IE2201), of whom 188 subjects received the study drug, and were included in the safety analysis population, with the exclusion of 1 subject from Study IE2101 (open-label extension phase) who was found to meet an exclusion criterion before the start of the administration. A total of 61 subjects was withdrawn from the study, with the main reasons (multiple reasons allowed) being others (e.g., nursing home admission, difficulty in visiting the study site) in 31 subjects and consent withdrawal in 20 subjects. The dose was reduced in 6 subjects during the study period.

The incidence of adverse events reported in this study was 88.8% (167 of 188 subjects), and the adverse events reported in ≥10% of subjects were nasopharyngitis (26.1% [49 subjects]), constipation (20.2% [38 subjects]), Alzheimer's disease (14.4% [27 subjects]), and fall (11.7% [22 subjects]).

Two subjects died (gastric cancer and dissecting aortic aneurysm/cardiac tamponade), and these deaths were both assessed as unrelated to the study drug. The incidence of serious adverse events was 18.6% (35 of 188 subjects). The serious adverse events reported in ≥2 subjects were pneumonia in 5 subjects, cerebral infarction in 4 subjects, femoral neck fracture in 3 subjects, and cataract, cholecystitis, bronchitis, fall, and pneumonia aspiration in 2 subjects each. A causal relationship to the study drug was not ruled out for cerebral infarction in 3 subjects and cholecystitis in 1 subject.

The following non-serious adverse events led to study drug discontinuation in 9 subjects: decreased

activity, incontinence, loss of consciousness, hypotension, dysphagia, urinary retention, generalised urticaria, asthenia, gastric ulcer, decreased appetite, dizziness, restlessness, dysuria, delirium, and excitability in 1 subject each.

4.(iii).A.(6).3) Long-term extension study of Studies IE2301, IE3501, and IE3604 (5.3.5.4.2; Study IE3503; Studied period, ongoing from [redacted] 20[redacted]; data cutoff, [redacted] 20[redacted]; reference data)

The long-term safety of memantine was investigated at 80 centers in Japan in an open-label study enrolling patients who had completed Study IE2301, IE3501, or IE3604 and wished to continue treatment.

Memantine was orally administered once daily after breakfast (if missed, the dose was taken before evening meal on the same day). Former subjects of Study IE2301 started treatment at a daily dose of 20 mg within 7 days after the last dose of Study IE2301. Former subjects of Study IE3501 were treated at a daily dose titrated from 5 mg to 20 mg in weekly increments of 5 mg. Former subjects of Study IE3604 started treatment at a daily dose of 20 mg on the day after the last dose of Study IE3604. The same dose titration as in the former subjects of Study IE3501 was required when the interval between the last dose in IE3604 and the first dose in this study exceeded 7 days. The dose was allowed to be reduced to 10 mg in the event that adverse events attributable to the dose level occurred during study treatment, and was allowed to be increased back to 20 mg when the adverse events resolved. The mean duration of treatment in this study was 497.5 days.

The main inclusion criterion was completion of Study IE2301, IE3501, or IE3604. Concomitant use of other investigational products was prohibited.

A total of 433 subjects (99, 314, and 20 subjects from Study IE2301, Study IE3501, and Study IE3501 via Study IE3604, respectively) were enrolled by the cutoff date, and included in the safety analysis population. A total of 211 subjects were withdrawn from the study, with the main reasons (multiple reasons allowed) being adverse events (80 subjects) and nursing home admission (59 subjects). The dose of memantine was reduced in 9 subjects[*] during the study period.

The incidence of adverse events reported in this study was 89.6% (388 of 433 subjects). The adverse events reported in ≥5% of subjects were nasopharyngitis (29.6% [128 of 433 subjects]), constipation (20.1% [87 of 433 subjects]), fall (19.6% [85 of 433 subjects]), contusion (10.2% [44 of 433 subjects]), diarrhoea (9.9% [43 of 433 subjects]), Alzheimer's disease (7.4% [32 of 433 subjects]), vomiting and insomnia (6.7% [29 of 433 subjects] for each event), dehydration (6.5% [28 of 433 subjects]), upper respiratory tract inflammation (6.0% [26 of 433 subjects]), decubitus ulcer and pyrexia (5.8% [25 of 433 subjects] for each event), oedema peripheral (5.5% [24 of 433 subjects]), and inappetence (5.3% [23 of 433 subjects]).

[*] As of [redacted], 20[redacted]

Nineteen subjects died due to the following adverse events: pneumonia, sepsis, and pneumonia aspiration (in 3 subjects each), cardio-respiratory arrest (in 2 subjects), cardiac failure acute, gastric ulcer, death, drowning, sudden death, cholecystitis, marasmus, colon cancer, lymphoma, metastatic hepatic cancer, cerebral haemorrhage, acute respiratory failure, and aspiration (in 1 subject each). Only pneumonia and sepsis were assessed as "possibly related" to the study drug because of the lack of detailed information about the clinical course. The incidence of serious adverse events was 30.9% (134 of 433 subjects). The serious adverse events reported in ≥3 subjects were pneumonia in 15 subjects, dehydration in 14 subjects, pneumonia aspiration in 12 subjects, femoral neck fracture in 11 subjects, cerebral infarction and urinary tract infection in 7 subjects each, femur fracture and inappetence in 5 subjects each, Alzheimer's disease, decubitus ulcer, cholecystitis, and sepsis in 4 subjects each, cerebral haemorrhage, cataract, infection, influenza, and decreased appetite in 3 subjects each.

The incidence of non-serious adverse events leading to study drug discontinuation was 4.6% (20 of 433 subjects). Among these events, those reported in ≥2 subjects were Alzheimer's disease in 3 subjects and agitation and anger in 2 subjects each.

Ophthalmologic examination detected no clinically relevant abnormalities.

4.(iii).A.(6).4) Long-term extension study in patients with mild to moderate AD (5.3.5.2.3; Study MA3302; Studied period, [redacted] 20[redacted] to [redacted] 20[redacted])

The long-term safety and efficacy of memantine were investigated at 59 centers in Japan in a randomized, parallel-group, comparative study enrolling patients who had completed Study MA3301 and wished to continue treatment (target sample size of 300 subjects).

Subjects received memantine once daily after breakfast (if missed, the dose was taken before evening meal on the same day) for 28 weeks. Subjects enrolled in this study were randomized into either Group A or Group B. During the first 4-week dose-titration phase (in a double-blind setting), subjects in Group A received memantine at a dose titrated from 5 mg to 20 mg in weekly increments of 5 mg, while subjects in Group B received memantine at a starting dose of 10 mg, which was increased to 20 mg at Week 3. During the dose-maintenance phase from Weeks 5 to 28, subjects received a daily dose of 20 mg in an open-label setting.

The main inclusion criterion was completion of Study MA3301. The requirements concerning the use of concomitant drugs were the same as those in Study MA3301, but there were no specific requirements concerning rehabilitation programs.

All of the 421 subjects enrolled in the study (broken down by the treatment groups in the dose-titration phase of the previous study: placebo group-Group A, 67 subjects; placebo group-Group B, 66 subjects; memantine 10 mg group-Group A, 75 subjects; memantine 10 mg group-Group B, 75 subjects; memantine 20 mg group-Group A, 69 subjects; and memantine 20 mg group-Group B, 69 subjects) were

included in the safety analysis population, and 413 subjects were included in the FAS, which was defined as the efficacy analysis population, with the exclusion of 8 subjects who had not been evaluated for efficacy after treatment (2 and 6 subjects in the former placebo and memantine 10 mg groups, respectively). The following subjects were withdrawn from the study during the dose-titration phase: 9 subjects (3 and 6 subjects in Group A and Group B, respectively, in the dose-titration phase) in the safety analysis population and 40 subjects (13, 17, and 10 subjects in the former placebo, memantine 10 mg, and memantine 20 mg groups, respectively) in the overall study population, with the main reasons being adverse events and request for withdrawal.

A LOCF analysis of the FAS yielded changes in the ADAS-J cog score at Week 12 and Week 28 of this study (score at each time point – score at baseline in this study) of 0.71 ± 4.10 (mean ± SD) and 2.75 ± 4.83, respectively, for the former placebo group, 0.85 ± 4.33 and 2.53 ± 4.67, respectively, for the former memantine 10 mg group, and 0.94 ± 3.95 and 2.54 ± 5.54, respectively, for the former memantine 20 mg group.

The incidence of adverse events during the dose-titration phase was 28.9% (61 of 211 subjects) in Group A and 30.5% (64 of 210 subjects) in Group B.

The overall incidence of adverse events during the study period (the dose-titration phase and the dose-maintenance phase) by treatment group in the previous study was 75.9% (101 of 133 subjects) in the former placebo group, 72.0% (108 of 150 subjects) in the former memantine 10 mg group, and 72.5% (100 of 138 subjects) in the former memantine 20 mg group. The adverse events reported in ≥3% of subjects in any group are shown in Table 5.

Table 5. Adverse events reported in ≥3% of subjects in any group
(by treatment group in the previous study)

	Former placebo group N = 133	Former memantine 10 mg group N = 150	Former memantine 20 mg group N = 138
Overall incidence	75.9 (101)	72.0 (108)	72.5 (100)
Nasopharyngitis	17.3 (23)	20.7 (31)	13.0 (18)
Dizziness	8.3 (11)	8 (5.3)	4.3 (6)
Fall	5.3 (7)	6.7 (10)	6.5 (9)
Hypertension	5.3 (7)	4.0 (6)	1.4 (2)
Contusion	3.0 (4)	4.0 (6)	3.6 (5)
Eczema	1.5 (2)	3.3 (5)	0.7 (1)
Cystitis	0.8 (1)	3.3 (5)	2.9 (4)
Weight decreased	0.8 (1)	3.3 (5)	1.4 (2)
Constipation	6.8 (9)	2.7 (4)	5.8 (8)
Diarrhoea	4.5 (6)	2.7 (4)	2.9 (4)
Blood creatine phosphokinase increased	2.3 (3)	2.7 (4)	3.6 (5)
Vomiting	3.8 (5)	2.0 (3)	2.2 (3)
Cataract	1.5 (2)	2.0 (3)	4.3 (6)
Headache	5.3 (7)	1.3 (2)	2.9 (4)
Blood triglycerides increased	3.8 (5)	1.3 (2)	3.6 (5)
Musculoskeletal pain	3.8 (5)	1.3 (2)	0.7 (1)
Dental caries	3.0 (4)	1.3 (2)	4.3 (6)
Excoriation	3.0 (4)	1.3 (2)	1.4 (2)
Back pain	1.5 (2)	1.3 (2)	4.3 (6)
Cough	0.8 (1)	1.3 (2)	3.6 (5)
Arthralgia	4.5 (6)	0.7 (1)	1.4 (2)
Blood pressure increased	3.0 (4)	0.7 (1)	3.6 (5)
Pruritus	3.0 (4)	0.7 (1)	0.7 (1)
Rash	5.3 (7)	0 (0)	1.4 (2)
Bronchitis	3.8 (5)	0 (0)	2.2 (3)

% (number of subjects)

Two subjects in the former memantine 10 mg group died (interstitial pneumonia and pancreatic neoplasm/metastases to liver/metastases to lymph nodes). Interstitial pneumonia is an event previously reported to be associated with the use of memantine, and in this case, a causal relationship to the study drug was not ruled out completely. However, the investigator assessed this event as being unlikely to be related to the study drug because of its extremely low incidence in Japanese clinical studies and in foreign countries (based on the data from clinical studies and those reported after the market launch), possible involvement of concomitant medications, and the mostly idiopathic nature of this event. The incidence of serious adverse events was 10.5% (44 of 421 subjects). A causal relationship to the study drug was not ruled out for the following serious non-fatal adverse events in 11 subjects: asthma/bronchitis, diabetes mellitus, dizziness, aortic dissection, hypertension, liver abscess, convulsion, cerebral infarction, gastric cancer, acute myocardial infarction, and lymphadenopathy.

The incidence of non-serious adverse events leading to study drug discontinuation was 1.4% (6 of 421 subjects).

Ophthalmologic examination (lens, cornea) was performed in a total of 220 subjects, and 3 subjects were assessed as “normal” or “abnormal (not clinically relevant)” at baseline and as “abnormal (clinically relevant)” at the final evaluation (lenticular abnormality in 2 subjects and corneal abnormality

in 1 subject).

4.(iii).A.(7) Foreign phase III studies

4.(iii).A.(7).1) Phase III study in patients with moderately severe to severe AD (5.3.5.1.6; Study MRZ90001-9605 [double-blind phase]; Studied period, [redacted] 19[redacted] to [redacted] 19[redacted])

A randomized, double-blind, parallel-group, comparative study was conducted in foreign patients with AD at 32 foreign centers to investigate the efficacy and safety of memantine in patients with moderately severe to severe AD (target sample size of 250 subjects, 125 subjects in each group). Subjects received oral doses of memantine 20 mg or placebo.

The study drug was administered twice daily after breakfast and lunch (if missed after lunch, the dose was taken no later than 14:00 on the same day) for 28 days. During the 3-week dose-titration phase, subjects in the memantine group received memantine at a dose titrated from 5 mg to 20 mg in weekly increments of 5 mg and then at 20 mg during the 25-week dose-maintenance phase.

The main inclusion criteria were generally the same as those in the late phase II study (Study IE2101 [double-blind phase]) except for the following:

- patients with an MMSE score of ≥3 and ≤14 and also at a FAST stage of ≥6a before the start of the double-blind phase; and
- patients with a severity score of 5 or 6 according to the Global Deterioration Scale (GDS).

Concomitant use of any drugs known to improve cognitive function, such as tacrine and donepezil, was prohibited, but there were no specific requirements concerning rehabilitation programs.

All of the 252 treated subjects (126 and 126 subjects in the placebo and memantine 20 mg groups, respectively) were included in the safety analysis population and the ITT population. Seventy-one subjects (42 and 29 subjects, respectively) were withdrawn from the study with the main reasons (multiple reasons allowed) being adverse events (22 and 13 subjects, respectively) and consent withdrawal (14 and 12 subjects, respectively). Primary efficacy analysis was performed on the ITT population by the LOCF approach.

The changes in the CIBIC-plus score (one of the primary endpoints) over time are shown in Figure 6. The change in CIBIC-plus score at Week 28 was 4.73 ± 1.07 (mean ± SD) in the placebo group and 4.48 ± 1.09 in the memantine 20 mg group, with no significant difference between the groups (P = 0.0644, Wilcoxon-Mann-Whitney test).

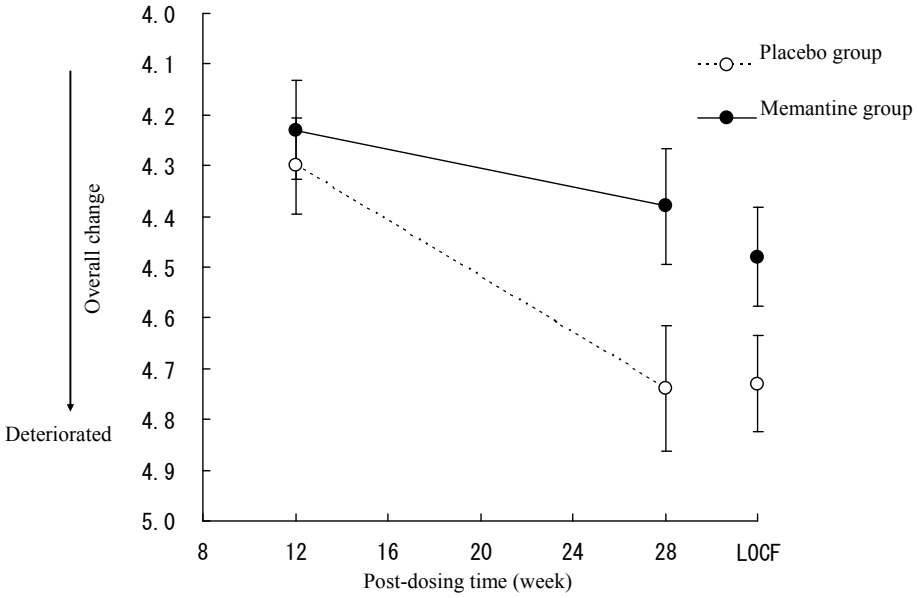


Figure 6. Changes in the CIBIC-plus score over time (ITT [OC and LOCF]) (mean ± standard error)

The changes in the score of ADCS-ADL$_{19}$ (the other primary endpoint) over time are shown in Figure 7. The mean ADCS-ADL$_{19}$ score at baseline was 27.43 in the placebo group and 26.84 in the memantine 20 mg group, and the change in the ADCS-ADL$_{19}$ score from baseline to Week 28 was −5.08 ± 6.30 (mean ± SD) in the placebo group and −3.02 ± 6.75 in the memantine 20 mg group. A significant difference between the treatment groups was detected in terms of changes in the ADCS-ADL$_{19}$ score from baseline to Week 28 (P = 0.0217, Wilcoxon-Mann-Whitney test).

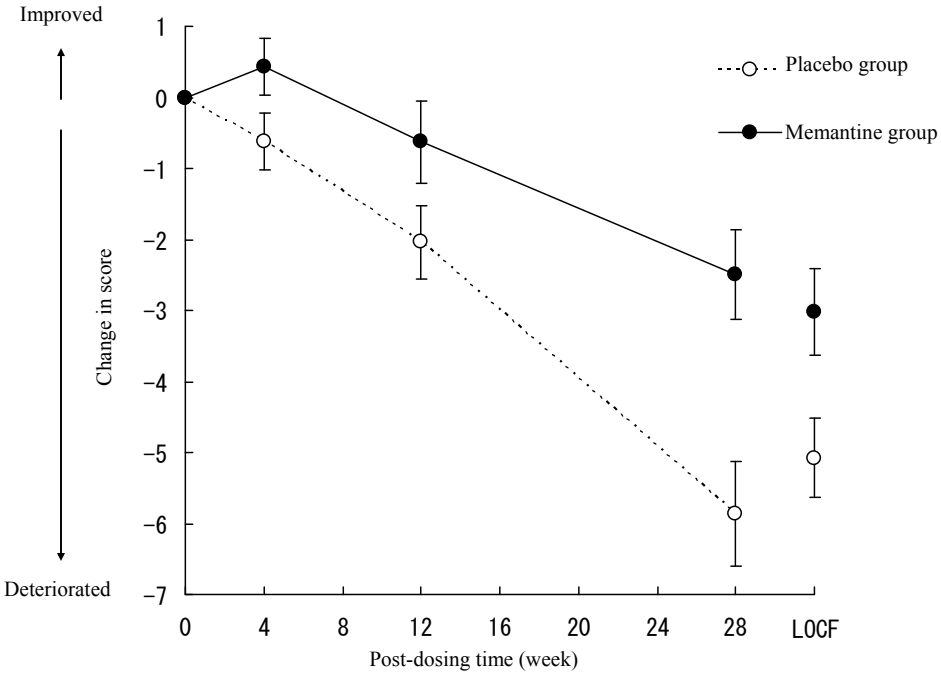


Figure 7. Changes in the ADCS-ADL$_{19}$ score over time (ITT [OC and LOCF]) (mean ± standard error)

The mean SIB score (one of the secondary endpoints) at baseline was 68.33 in the placebo group and 65.86 in the memantine 20 mg group. The change in the SIB score from baseline to Week 28 was −9.84 ± 13.43 (mean ± SD) in the placebo group and −3.93 ± 11.26 in the memantine 20 mg group, with a significant difference between the groups (P = 0.0003, Wilcoxon-Mann-Whitney test).

The incidence of adverse events was 86.5% (109 of 126 subjects) in the placebo group and 84.1% (106 of 126 subjects) in the memantine 20 mg group. The adverse events reported in ≥5% of subjects in either group are shown in Table 6.

Table 6. Adverse events reported in ≥5% of subjects in either group

	Placebo group N = 126	Memantine 20 mg group N = 126
Overall incidence	86.5 (109)	84.1 (106)
Agitation	31.7 (40)	18.3 (23)
Urinary incontinence	11.1 (14)	11.1 (14)
Insomnia	7.9 (10)	10.3 (13)
Diarrhoea	7.9 (10)	9.5 (12)
Hallucination	3.2 (4)	8.7 (11)
Injury	8.7 (11)	7.9 (10)
Inappetence	2.4 (3)	7.9 (10)
Fall	7.1 (9)	7.1 (9)
Vomiting	3.2 (4)	7.1 (9)
Headache	2.4 (3)	6.3 (8)
Urinary tract infection	13.5 (17)	5.6 (7)
Constipation	7.9 (10)	5.6 (7)
Cough	7.9 (10)	5.6 (7)
Faecal incontinence	5.6 (7)	5.6 (7)
Somnolence	4.8 (6)	5.6 (7)
Dizziness	2.4 (3)	5.6 (7)
Upper respiratory tract infection	7.1 (9)	4.8 (6)
Confusion	6.3 (8)	3.2 (4)

% (number of subjects)

Five subjects in the placebo group died (AD in 2 subjects; and thyroid neoplasm malignant, pneumonia, and cerebrovascular disorder in 1 subject each), and 2 subjects in the memantine 20 mg group died (myocardial infarction in 2 subjects). All of these events were assessed as “unrelated” or “unlikely related” to the study drug. The incidence of serious adverse events was 18.3% (23 of 126 subjects) in the placebo group and 12.7% (16 of 126 subjects) in the memantine 20 mg group. All of the serious adverse events observed were assessed as “probably related” or “possibly related” to the study drug. There were no serious adverse events reported in ≥2 subjects in either group.

The incidence of adverse events leading to study drug discontinuation was 17.5% (22 of 126 subjects) in the placebo group and 10.3% (13 of 126 subjects) in the memantine 20 mg group. Among these adverse events, agitation had the highest incidence (7 subjects in the placebo and 6 subjects in the memantine 20 mg groups).

4.(iii).A.(7).2) Phase III study in patients with moderate to severe AD (5.3.5.1.7; Study MEM-MD-02; Studied period, [redacted] 20[redacted] to [redacted] 20[redacted])

A randomized, double-blind, parallel-group, comparative study was conducted in foreign patients with AD at 37 foreign centers to investigate the efficacy and safety of memantine in patients with moderate to severe AD being treated with donepezil (target sample size of 340 subjects, 170 subjects in each group). Subjects received oral doses of memantine 20 mg or placebo.

The study drug was administered twice daily in the morning and afternoon. Subjects received placebo during the run-in period (1 to 2 weeks), and in the subsequent double-blind phase (24 weeks), subjects in the memantine group received memantine at a daily dose titrated from 5 mg to 20 mg in weekly increments of 5 mg.

The patients included in the study were those who were outpatients aged ≥50 years and who met the inclusion criteria such as the following:

(a) patients meeting the diagnostic criteria for probable Alzheimer's disease according to the NINCDS-ADRDA;
(b) patients whose CT or MRI findings obtained during the 12 months before screening were consistent with a diagnosis of probable AD;
(c) patients with an MMSE score of ≥5 and ≤14 both at the screening and at the start of the double-blind phase;
(d) patients who had received donepezil during the 6 months before screening, at a constant dose of 5 to 10 mg during the last 3 months; and
(e) patients who had a knowledgeable and reliable caregiver, and who were able to be accompanied by the same caregiver at every study visit throughout the study period.

Concomitant use of cholinesterase inhibitors other than donepezil was prohibited, but there were no requirements concerning rehabilitation programs.

All of the 403 treated subjects (201 and 202 subjects in the placebo and memantine 20 mg groups, respectively) were included in the safety analysis population, and 395 subjects (197 and 198 subjects, respectively) who were evaluated for the primary endpoints before and at least once during study drug administration were included in the ITT population. Eighty-one subjects (51 and 30 subjects, respectively) were withdrawn from the study with the main reasons (multiple reasons allowed) being adverse events (25 and 15 subjects, respectively) and consent withdrawal (16 and 8 subjects, respectively). Primary efficacy analysis was performed on the ITT population by the LOCF method.

The mean SIB score (one of the primary endpoints) at baseline was 79.8 in the placebo group and 77.8 in the memantine 20 mg group. The change in the SIB score from baseline to Week 24 was −2.5 ± 0.69 (least squares mean* ± standard error) in the placebo group and 0.9 ± 0.67 in the memantine 20 mg group, with a significant difference between the groups ($P < 0.001$, analysis of covariance*).

* ANCOVA model including treatment group and study center as factors and baseline score as a covariate

The mean ADCS-ADL$_{19}$ score (the other primary endpoint) at baseline was 36.2 in the placebo group and 35.9 in the memantine 20 mg group. The change in the ADCS-ADL$_{19}$ score from baseline to Week 24 was −3.4 ± 0.51 (least squares mean* ± standard error) in the placebo group and −2.0 ± 0.50 in the memantine 20 mg group, with a significant difference between the groups (P = 0.028, analysis of covariance*).

The CIBIC-plus score (one of the secondary endpoints) at Week 24 was 4.66 ± 1.05 (mean ± SD) in the placebo group and 4.41 ± 1.05 in the memantine 20 mg group, with a significant difference between the groups (P = 0.027, Cochran-Mantel Haenszel test using modified ridit scores adjusted for institutional factors).

The incidence of adverse events was 71.6% (144 of 201 subjects) in the placebo group and 78.2% (158 of 202 subjects) in the memantine 20 mg group. The adverse events reported in ≥5% of subjects in either group are shown in Table 7.

Table 7. Adverse events reported in ≥5% of subjects in either group

	Placebo group N = 201	Memantine 20 mg group N = 202
Overall incidence	71.6 (144)	78.2 (158)
Agitation	11.9 (24)	9.4 (19)
Confusion	2.0 (4)	7.9 (16)
Fall	7.0 (14)	7.4 (15)
Flu like symptoms	6.5 (13)	7.4 (15)
Dizziness	8.0 (16)	6.9 (14)
Headache	2.5 (5)	6.4 (13)
Urinary tract infection	5.0 (10)	5.9 (12)
Urinary incontinence	3.0 (6)	5.4 (11)
Injury	8.0 (16)	5.0 (10)
Upper respiratory tract infection	6.5 (13)	5.0 (10)
Oedema peripheral	4.0 (8)	5.0 (10)
Diarrhoea	8.5 (17)	4.5 (9)
Faecal incontinence	5.0 (10)	2.0 (4)

% (number of subjects)

Two subjects in the placebo group died (lung cancer and myocardial infarction), and 1 subject in the memantine 20 mg group died (myocardial infarction); however, a causal relationship to the study drug was ruled out for all of these events. The incidence of serious adverse events was 10.0% (20 of 201 subjects) in the placebo group and 12.4% (25 of 202 subjects) in the memantine 20 mg group. These events were assessed as “probably related” or “possibly related” to the study drug. There were no serious adverse events reported in ≥2 subjects in either group.

The incidence of adverse events leading to study drug discontinuation was 12.4% (25 of 201 subjects) in the placebo group and 7.4% (15 of 202 subjects) in the memantine 20 mg group. Among these events, confusion had the highest incidence (3 subjects in the placebo and 4 subjects in the memantine 20 mg groups).

4.(iii).A.(7).3) Phase III study in patients with moderate to severe AD (5.3.5.1.8; Study MEM-MD-01; Studied period, [redacted] 20[redacted] to [redacted] 20[redacted])

A randomized, double-blind, parallel-group, comparative study was conducted in foreign patients with AD at 37 foreign centers to investigate the efficacy and safety of memantine in patients with moderate to severe AD (target sample size of 340 subjects, 170 subjects in each group). Subjects received oral doses of memantine 20 mg or placebo.

The study drug was administered twice daily in the morning and afternoon. Subjects received placebo during the run-in period (1 to 2 weeks), and in the subsequent double-blind phase (24 weeks), subjects in the memantine group received memantine at a daily dose titrated from 5 mg to 20 mg in weekly increments of 5 mg.

The main inclusion criteria were the same as those in Study MEM-MD-02 except for the requirements concerning the use of donepezil. Concomitant use of drugs known to improve cognitive function, such as donepezil, was prohibited. There were no specific requirements concerning rehabilitation programs.

All of the 350 treated subjects (172 and 178 subjects in the placebo and memantine 20 mg groups, respectively) were included in the safety analysis population, and 336 subjects (165 and 171 subjects, respectively) who were evaluated for the primary endpoints before and at least once during study drug administration were included in the ITT population. Ninety subjects (46 and 44 subjects, respectively) were withdrawn from the study, with the main reasons being adverse events (23 and 22 subjects, respectively) and consent withdrawal (13 and 13 subjects, respectively). Primary efficacy analysis was performed on the ITT population by the LOCF approach.

The mean SIB score (one of the primary endpoints) at baseline was 75.6 in the placebo group and 77.2 in the memantine 20 mg group. The change in the SIB score from baseline to Week 24 was −2.5 ± 1.0 (least squares mean* ± standard error) in the placebo group and −2.0 ± 1.0 in the memantine 20 mg group, with no significant difference between the groups (P = 0.616, analysis of covariance*).

The mean ADCS-ADL_{19} score (the other primary endpoint) at baseline was 33.6 in the placebo group and 33.1 in the memantine 20 mg group. The change in the ADCS-ADL_{19} score from baseline to Week 24 was −2.7 ± 0.6 (least squares mean* ± standard error) in the placebo group and −2.0 ± 0.6 in the memantine 20 mg group, with no significant difference between the groups (P = 0.282, analysis of covariance*).

The CIBIC-plus score (one of the secondary endpoints) at Week 24 was 4.6 ± 1.0 (mean ± SD) in the placebo group and 4.3 ± 1.0 in the memantine 20 mg group, with no significant difference between the groups (P = 0.182, Cochran-Mantel Haenszel test using modified ridit scores adjusted for institutional

* ANCOVA model including treatment group and study center as factors and baseline score as a covariate

factors).

The incidence of adverse events was 72.7% (125 of 172 subjects) in the placebo group and 73.6% (131 of 178 subjects) in the memantine 20 mg group. The adverse events reported in ≥5% in either group are shown in Table 8.

Table 8. Adverse events reported in ≥5% of subjects in either group

	Placebo group N = 172	Memantine 20 mg group N = 178
Overall incidence	72.7 (125)	73.6 (131)
Agitation	14.0 (24)	9.0 (16)
Hypertension	2.3 (4)	7.9 (14)
Dizziness	6.4 (11)	6.7 (12)
Oedema peripheral	4.7 (8)	6.7 (12)
Constipation	4.7 (8)	6.2 (11)
Fall	9.9 (17)	5.6 (10)
Injury	7.6 (13)	5.6 (10)
Flu like symptoms	4.7 (8)	5.6 (10)
Diarrhoea	4.7 (8)	5.6 (10)
Anxiety	3.5 (6)	5.6 (10)
Urinary tract infection	5.2 (9)	5.1 (9)
Confusion	4.7 (8)	5.1 (9)
Depression	2.9 (5)	5.1 (9)
Insomnia	5.2 (9)	2.2 (4)
Headache	6.4 (11)	1.7 (3)

% (number of subjects)

Three subjects in the placebo group died (cardiac failure, Alzheimer's disease/dehydration, and Alzheimer's disease/aspiration), and 5 subjects in the memantine 20 mg group died (cardiac arrest in 2 subjects, pneumonia, ventricular tachycardia, and death). The only fatal adverse events assessed by the investigator as "possibly related" to the study drug were Alzheimer's disease and /aspiration reported in 1 subject in the placebo group. The incidence of serious adverse events was 16.9% (29 of 172 subjects) in the placebo group and 14.6% (26 of 178 subjects) in the memantine 20 mg group. These events were assessed as "probably related" or "possibly related" to the study drug. There were no serious adverse events reported in ≥2 subjects in either group.

The incidence of adverse events leading to study drug discontinuation was 13.4% (23 of 172 subjects) in the placebo group and 12.4% (22 of 178 subjects) in the memantine 20 mg group. Among these events, agitation had the highest incidence (6 and 3 subjects in the placebo and memantine 20 mg groups, respectively).

4.(iii).B Outline of the review by PMDA

4.(iii).B.(1) Clinical positioning

PMDA asked the applicant to explain the clinical positioning of memantine.

The applicant responded as follows:

Memantine has been marketed in 70 countries mainly for the indication of moderate to severe AD.

Memantine is recognized as a standard treatment for AD in medical literature, including the American Psychiatric Association's guideline (American Psychiatric Association. *Practice Guideline for the Treatment of Patients with Alzheimer's Disease and Other Dementias*. 2nd ed. 2007:1-85), Harrison's Principles of Internal Medicine (Bird TD, et al., eds. Harrison's *Principles of Internal Medicine.* 17th ed. McGraw Hill. 2008;2536-49), and Cecil Medicine (Knopman DS. Alzheimer's disease and other dementias. In: Goldman L, Ausiello D, eds. *Cecil Medicine*. 23rd ed. Saunders Elsevier. 2007;2667-76), and it is widely used in clinical practice. Outside Japan, in particular in the US and Europe, 3 AChE inhibitors (donepezil, galantamine hydrobromide, and rivastigmine tartrate) and an NMDA receptor channel antagonist (memantine) have been widely used for the treatment of AD. Memantine is used as an early and later treatment in patients already with moderate to severe AD who are unresponsive to AChE inhibitors or intolerant of AChE inhibitors due to adverse drug reactions or those who have become refractory to AChE inhibitors because of exacerbation of symptoms. In these patients, memantine can be used as a replacement drug or in combination with AChE inhibitors. Although donepezil is the only drug currently marketed in Japan for the treatment of AD, the clinical positioning of memantine is considered not to differ significantly between in Japan and in foreign countries. Given that its mechanism of action is distinct from that of donepezil, which is the existing treatment option, memantine is believed to offer a new treatment option for patients with moderate to severe AD, and to thereby extend the treatment spectrum for the disease.

PMDA considers as follows:

The applicant's view on the clinical positioning of memantine is generally acceptable. However, no information is available on its use in combination with donepezil in Japanese patients with AD. The efficacy and safety of this combination are expected to be clarified through its future clinical use. Therefore, the applicant should actively collect and provide relevant information.

4.(iii).B.(2) Efficacy

4.(iii).B.(2).1) Methods used to evaluate the efficacy of anti-AD drugs

The applicant provided the following explanations on the standard methods used to evaluate the therapeutic effects of anti-AD drugs:

The methods used in Japanese clinical studies to evaluate the efficacy of memantine in AD have been established with reference to those for clinical evaluation of anti-AD drugs in the US and Europe and to those used in foreign clinical studies. In the US, superiority over an appropriate control drug needs to be demonstrated according to the Guidelines for the Clinical Evaluation of Antidementia Drugs (first draft; dated November 8, 1990, prepared by the Food and Drug Administration), in terms of 2 primary efficacy endpoints: cognitive function impairment (the core symptom of AD), and overall clinical status (or severity). In Europe, superiority over an appropriate control drug needs to be demonstrated according to the Note for Guidance on Medicinal Products in the Treatment of Alzheimer's Disease* (EMEA Guideline, London, Sep. 1997, CPMP/EWP/553/95 corrected), in terms of 2 of the following 3 primary

* In the revision in 2008, cognitive function and activities of daily living are listed as primary endpoints and overall clinical status as a secondary endpoint.

endpoints: cognitive function impairment (the core symptom of AD), activities of daily living, and overall clinical status. The following objective measures are commonly used for evaluation of cognitive function in clinical studies: ADAS-cog (Mohs RC, et al. *Psychopharmacol Bull*. 1983;19:448-50; Rosen WG, et al. *Am J Psychiatry*. 1984;141:1356-64) for mild to moderate AD; SIB (Panisset M, et al. *Arch Neurol*. 1994;51:41-5; Niina R, et al.*Japanese Journal of Geriatric Psychiatry*. 2005;16:683-91) for moderate to severe AD; and CIBIC-plus (Honma A, et al. *Japanese Journal of Geriatric Psychiatry*. 1997;8:855-69; Honma A, et al. *Japanese Journal of Geriatric Psychiatry*. 1999;10:193-229) for overall clinical status irrespective of severity of AD.

SIB-J scores were used for evaluation of cognitive function in the 2 main Japanese studies (Study IE2101 [double-blind phase] and Study IE3501). CIBIC plus-J and ADCS ADL-J scores were used for evaluation of overall clinical status and activities of daily living in Study IE2101 (double-blind phase). However, the results of Study IE2101 (double-blind phase) suggested that the use of DAD, a subscale of CIBIC plus-J, was unsuitable for the evaluation of patients with severe AD because many of its assessment variables, such as cooking, making phone calls, monetary transactions, and communication, are not undertaken by this patient population on a daily basis, and that proper evaluation by ADCS ADL-J was not feasible without a caregiver capable of performing detailed observation of the patient's activities of daily living. Consequently, Study IE3501 employed the Modified CIBIC plus-J, a modified version of CIBIC plus-J incorporating FAST instead of the DAD subscale, for evaluation of overall clinical status. ADCS ADL-J was not used.

PMDA sees no particular problem in using SIB-J and ADCS ADL-J scores as the primary endpoints and CIBIC plus-J scores as the secondary endpoint in Study IE2101 (double-blind phase) and in using SIB-J and Modified CIBIC plus-J scores as the primary endpoints in Study IE3501.

4.(iii).B.(2).2) Efficacy of memantine in double-blind comparative studies

(a) Efficacy of memantine shown in evaluation of overall clinical status

The applicant provided the following explanations for the failure of the 2 main Japanese studies to demonstrate the efficacy of memantine in terms of CIBIC plus-J scores:

In Study IE2101 (double-blind phase), a significant difference between the memantine group and the placebo group was detected in terms of SIB-J scores but not in terms of ADCS ADL-J scores, the other primary endpoint, or CIBIC plus-J scores, a secondary endpoint. The results of subgroup analyses indicated that the memantine efficacy data were mainly affected by the gender of caregivers and the use of outpatient care and rehabilitation services. Therefore, it was planned that Study IE3501 would incorporate a number of specific measures, such as additional requirements for caregivers in an inclusion criterion to ensure that observation of the subject's activities of daily living (e.g., in principle, during a daytime stay on ≥3 days every week) was adequate in order to improve the quality of information from caregivers, which was pivotal in evaluation by CIBIC plus-J. Nevertheless, Study IE3501 also failed to demonstrate the efficacy of memantine in patients with severe AD in terms of Modified CIBIC plus-J scores. Subgroup analyses of the results of the Modified CIBIC plus-J evaluation in Study IE3501

suggested that, again in this study, the efficacy data based on Modified CIBIC plus-J scores were affected by the classification of caregivers and the use of outpatient care and rehabilitation services.
In addition, the results of evaluation of overall clinical status in the 2 studies revealed:

(1) In a subgroup in which the caregivers were the subjects' wives, a significant difference was shown between the placebo and memantine 20 mg groups, whereas the difference was smaller in the subgroup who received outpatient care or rehabilitation service than in the subgroup who did not; and

(2) A subgroup in which the subjects did not receive outpatient care or rehabilitation services showed a significant difference between the placebo and memantine 20 mg groups (Table 9), where the difference was shown not only in the subgroup whose caregivers were the subjects' wives but also to some extent in the subgroup whose caregivers were not the subjects' wives.

These findings were interpreted as suggesting that the use of outpatient care and rehabilitation services was the main factor affecting the CIBIC plus-J evaluation in the 2 main Japanese studies. The use of outpatient care and rehabilitation services is considered to have prevented the CIBIC plus-J evaluators from fully noticing changes in clinical symptoms while they were actually occurring, and given the high percentage of the use of these services in Japan (42.0% in Study IE2101 [double-blind phase] and 55.3% in Study IE3501), this is a conceivable reason for the failure to detect a significant difference in CIBIC plus-J scores between the treatment groups. However, the applicant considered that this factor have influenced the CIBIC plus-J evaluation but not to have an effect on the efficacy of memantine.

Table 9. Subgroup analysis of the effect of outpatient care and rehabilitation services on CIBIC plus-J scores in the 2 main Japanese studies (OC)

Receiving outpatient care or rehabilitation services	Treatment group	Study IE2101 (double-blind phase)			Study IE3501		
		Number of subjects	Mean ± SD	*P*-value[a)]	Number of subjects	Mean ± SD	*P*-value[a)]
No	Placebo group	51	4.84±1.27	0.0338	83	4.69±0.94	0.0260
	Memantine 20 mg group	49	4.18±1.75		90	4.33±1.11	
Yes	Placebo group	34	4.47±1.35	0.6644	94	4.49±1.07	0.4583
	Memantine 20 mg group	34	4.62±1.46		100	4.60±1.02	

a) Mantel test

PMDA asked the applicant to discuss whether or not outpatient care and rehabilitation services per se had a greater effect than the efficacy of memantine on CIBIC plus-J scores in subjects receiving these services, and whether or not the effect of an increase in the incidence or severity of any specific adverse events on the CIBIC plus-J evaluation masked the efficacy of memantine.

The applicant explained as follows:

Short-term intensive rehabilitation programs for dementia, such as in outpatient care and rehabilitation services, have been reported to be effective for improving the quality of activities of daily living in patients with dementia by preventing the progression of severity of dementia and helping patients to maintain mental health (motivation and activeness). These programs are expected to facilitate return to life at home or an equivalent through relief of peripheral symptoms. It has also been reported, albeit not

necessarily supported by accumulated scientific data, that in some cases, rehabilitation programs are effective for enhancing emotional expression, initiative, and willingness as well as activating remaining functions (Hasegawa K. *Japanese Journal of Geriatric Psychiatry*. 1995;6:1035-42; Kurasawa T. *Japanese Journal of Geriatric Psychiatry*. 2000;11:1025-31; Endo H. *Japanese Journal of Geriatrics*. 2007;44:429-32). However, the following explanation is based on an investigation of the effect of outpatient care and rehabilitation services on CIBIC plus-J scores: the use of outpatient care and rehabilitation services reduced the time caregivers had to observe subjects, which resulted in losses in the quantity and accuracy of information on the subjects' activities of daily living and clinical status, and "evaluators of overall clinical status (CIBIC plus-J) were prevented from fully noticing changes in clinical symptoms while they were actually occurring, and failed to provide appropriate evaluation." This view is also presented in a report: "Investigation of the effects of nursing care services on changes of status of nursing care for patients with dementia, and consideration of the effect on CIBIC-plus by these changes" (Nakamura Y. *Japanese Journal of Geriatric Psychiatry*. 2010;21:685-94). In the 2 main Japanese studies, a significant difference between the placebo and memantine 20 mg groups was detected in the subgroup not receiving outpatient care or rehabilitation service (Table 9). Similar results have been obtained in the 3 main foreign studies (Study MRZ90001-9605 [double-blind phase], Study MEM-MD-02, and Study MEM-MD-01), in which the percentage of the use of these services was as low as 9.1% to 13.9%. During the 2 main Japanese studies, no subjects experienced the onset or persistence of any specific adverse events that could affect the individual observation items of CIBIC plus-J. Therefore, it is very unlikely that an increase in the incidence or severity of specific adverse events would have had an effect on the CIBIC plus-J evaluation, and would therefore not be a causal factor for the failure to show the efficacy of memantine.

In the 2 main Japanese studies, a significant difference between the placebo and memantine 20 mg groups was not detected in terms of overall clinical status (CIBIC plus-J), but was detected in terms of cognitive function (SIB-J). Given that peripheral symptoms in patients with AD occur secondary to cognitive function impairment, which is the core symptom of AD, prevention of exacerbation of cognitive function impairment may prevent the onset or exacerbation of secondary peripheral symptoms, leading to overall clinical benefits.

The Behave-AD scale is a subscale of CIBIC plus-J for the assessment of behavioral and psychological symptoms of dementia (BPSD). In the 2 main Japanese studies, albeit not chosen as an efficacy endpoint, the changes in the Behave-AD score at Week 24 were higher in the memantine 20 mg group than in the placebo group. A significant intergroup difference in Behave-AD scores was detected by LOCF analysis. The Behave-AD evaluation depends on information from caregivers. BPSD include many symptoms that are likely to be remembered by caregivers because they are difficult to handle and that are also likely to be reported to caregivers by other family members or workers at outpatient care and rehabilitation facilities. Given that efficacy was suggested by the Behave-AD evaluation, the efficacy of memantine can be confirmed based on the types of or changes in BPSD even in patients receiving outpatient care or rehabilitation services.

The above discussions indicate that the use of outpatient care and rehabilitation services affected the CIBIC-plus evaluation, but not the efficacy of memantine, and that memantine may possibly offer overall clinical benefits even in patients receiving outpatient care or rehabilitation services.

(b) Comparison of efficacy between foreign and Japanese clinical studies

The applicant discussed the pharmacokinetics of memantine, the results of the 2 main Japanese studies and 3 main foreign studies, and the effects of intrinsic and extrinsic ethnic factors on the efficacy and safety of memantine as follows, and then explained that the data from the 3 main foreign studies support the efficacy of memantine in Japanese patients with AD.

i) Memantine is unlikely to be affected by intrinsic ethnic factors due to its pharmacological properties, and is also unlikely to be affected by extrinsic ethnic factors. Nevertheless, differences in the availability of a public nursing care insurance program between in and outside Japan resulted in differences in the nursing care environment (e.g., prevalence of the use of outpatient care and rehabilitation services), as a part of medical practice.

ii) The efficacy of memantine shown by cognitive function evaluation (SIB) was similar between Japanese and foreign patients, and is therefore unlikely to be affected by ethnic factors (Table 10).

Table 10. Changes in the SIB score in the 2 main Japanese studies and 3 main foreign studies (LOCF)

		IE2101 (Double-blind phase)	IE3501	MRZ900001 -9605[a)] (Double-blind phase)	MEM-MD-02	MEM-MD-01
Placebo group	Number of subjects	107	206	126	196	165
	Mean ± SD	−3.42 ± 9.84	−4.87 ± 11.66	−9.84 ± 13.43	−2.30 ± 8.99	−2.64 ± 8.59
Memantine 20 mg group	Number of subjects	100	218	126	198	170
	Mean ± SD	0.10 ± 6.54	−0.42 ± 9.87	−3.93 ± 11.26	1.05 ± 7.94	−1.75 ± 11.44
Difference from the placebo group	Difference in mean (95% CI)	3.52 (1.21, 5.83)	4.46 (2.40, 6.51)	5.91 (2.84, 8.99)	3.35 (1.67, 5.03)	0.89 (−1.29, 3.07)
P-value		0.0051[b)]	< 0.0001[b)]	0.0003[b)]	< 0.001[c)]	0.616[c)]

a: Secondary endpoint
b: Wilcoxon rank sum test; c: Least squares mean difference test based on an ANCOVA model

iii) A difference in overall clinical status (CIBIC-plus) was found between Japanese and foreign patients, reflecting a difference in the nursing care environment (prevalence of the use of outpatient care and rehabilitation services) between Japan and foreign countries (Table 11). A high percentage of patients use outpatient care and rehabilitation services in Japan, and the use of these services affected the results of the 2 main Japanese studies (Table 9).

Table 11. CIBIC-plus scores at the final evaluation in the 2 main Japanese studies and the 3 main foreign studies (LOCF)

		IE2101[a] (Double-blind phase)	IE3501	MRZ900001 -9605[a] (Double-blind phase)	MEM-MD-02[a]	MEM-MD-01[a]
Placebo group	Number of subjects	107	208	126	196	163
	Mean ± SD	4.62 ± 1.26	4.65 ± 1.04	4.73 ± 1.07	4.66 ± 1.05	4.56 ± 1.04
Memantine 20 mg group	Number of subjects	100	217	126	198	171
	Mean ± SD	4.38 ± 1.55	4.48 ± 1.08	4.48 ± 1.09	4.41 ± 1.05	4.35 ± 1.03
Difference from the placebo group	Difference in mean (95% CI)	−0.24 (−0.62, 0.15)	−0.17 (−0.37, 0.04)	−0.25 (−0.51, 0.02)	−0.25 (−0.46, -0.04)	−0.22 (−0.44, 0.00)
P-value		0.3392[b]	0.1083[c]	0.0644[b]	0.027[d]	0.182[d]

a: Secondary endpoint
b: Wilcoxon rank sum test; c: Mantel test; d: Cochran-Mantel Haenszel test

iv) In the 2 main Japanese studies, a significant difference was detected between the placebo and memantine groups in the subgroup not receiving outpatient care or rehabilitation services (Table 9). The changes in the CIBIC-plus score over time in this subgroup were similar to those obtained by the pooled analysis of the 3 main foreign studies conducted in societies in which a smaller percentage of patients with AD received outpatient care or rehabilitation services.

v) As discussed in 4.(iii).B.(2).2).(a), the CIBIC-plus evaluators might have been unable to fully notice the actual changes in the clinical symptoms of subjects receiving outpatient care or rehabilitation services. The large percentage of subjects receiving outpatient care or rehabilitation services in Japan is thought to be responsible for the failure to detect a significant difference in CIBIC-plus scores. However, this factor might have influenced the CIBIC plus-J evaluation but not affected the efficacy of memantine.

vi) The pharmacokinetic profiles of memantine in patients with AD are not considered to differ significantly between Japanese and foreign populations.

vii) The safety profiles of memantine were similar between Japanese and foreign patients, with no Japanese-specific safety risks identified [see "4.(iii).A Summary of the submitted data"].

PMDA asked the applicant to explain why the applicant considers that the efficacy of memantine in patients with AD is unlikely to be affected by extrinsic ethnic factors while attributing the difference in CIBIC-plus scores, one of the primary endpoints, between Japanese and foreign subjects to the difference in the nursing care environment (prevalence of the use of outpatient care and rehabilitation services).

The applicant explained as follows:

The use of outpatient care and rehabilitation services may have affected the CIBIC-plus evaluation. Also, the difference detected in CIBIC-plus scores between Japanese and foreign subjects was attributable to the difference in the nursing care environment (prevalence of outpatient care and rehabilitation services) between Japan and foreign countries. Since this difference in the nursing care environment is not considered to have affected the efficacy of memantine in patients with AD, the efficacy of memantine is unlikely to be affected by extrinsic ethnic factors.

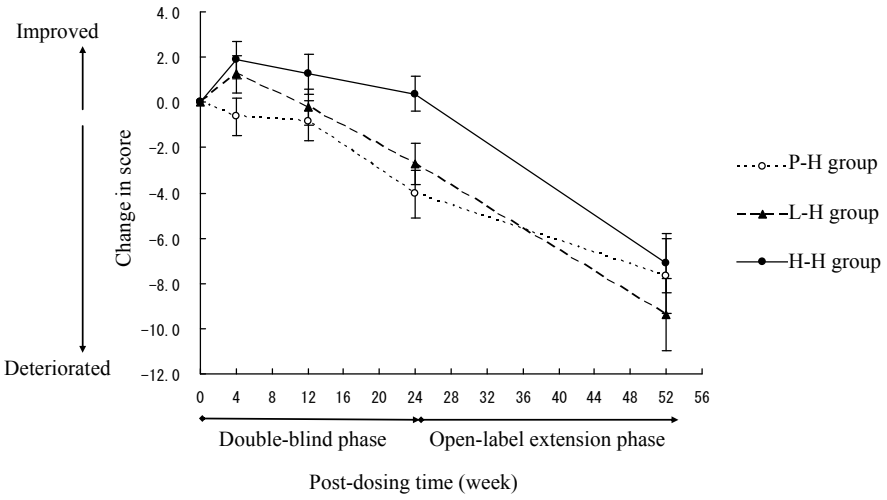
Taking account of Sections 4.(iii).B.(2).2).(a) and 4.(iii).B.(2).2). (b), PMDA considers as follows:
The efficacy of memantine as an anti-AD drug should be demonstrated in Japan, as in foreign countries, by its superiority over placebo in terms of 2 endpoints; cognitive function and overall clinical status or activities of daily living. Neither of the 2 main Japanese studies showed the superiority of memantine over placebo in terms of CIBIC plus-J scores (or ADCS ADL-J scores). Therefore, it cannot be concluded that the efficacy of memantine has been demonstrated in Japanese patients with AD. In addition, the applicant explained that the CIBIC plus-J evaluation was unable to demonstrate the efficacy of memantine because of the effects of outpatient care and rehabilitation services. Although PMDA does not deny the possibility that outpatient care and rehabilitation services were a factor affecting the CIBIC plus-J evaluation, the applicant's explanation was based solely on the results of post hoc subgroup analyses, and this does not provide sufficiently strong evidence to conclude that the potential efficacy of memantine did not be detected because of the effects of outpatient care and rehabilitation services. Nevertheless, due consideration should be given to the current status of AD treatment in Japan, where treatment options available for patients with AD are very limited. Given that the efficacy of memantine 20 mg in treating cognitive function impairment, one of the core symptoms of AD, was demonstrated in the 2 main Japanese studies; that the efficacy of memantine 20 mg has been demonstrated in foreign clinical studies, though bridging between Japanese and foreign studies was not successful; and that memantine has been established as a standard therapeutic drug for treating patients with AD in foreign countries, it can be expected that memantine will also be effective to some extent in Japanese patients with AD.

A final decision will be made on the approval for memantine, taking account of comments from the Expert Discussion.

4.(iii).B.(2).3) Efficacy of long-term treatment

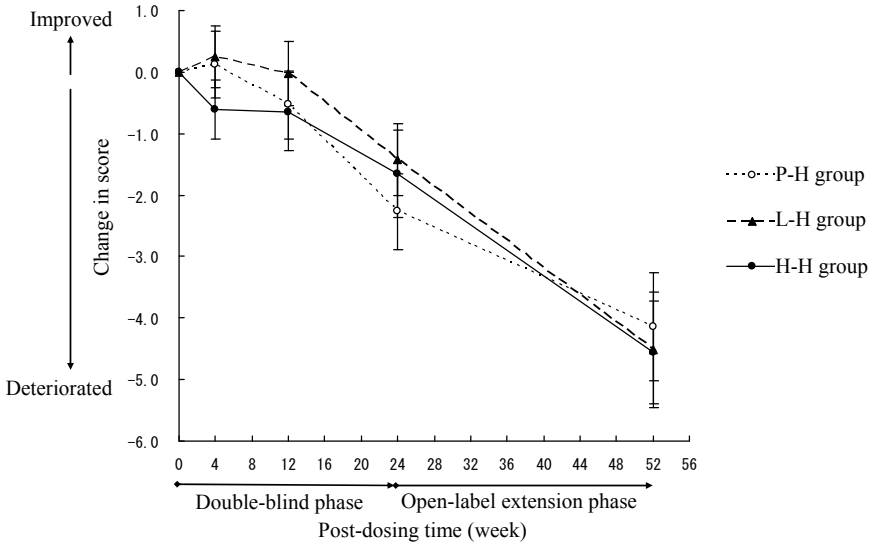
PMDA asked the applicant to explain the efficacy of long-term treatment with memantine, taking account of the results of Japanese long-term studies.

The applicant explained as follows:
The changes in the SIB-J and ADCS ADL-J scores over time in a Japanese long-term study (Study IE2101 [double-blind phase and open-label extension phase, 52 weeks in total]) are shown in the figures below.



P-H group, placebo-memantine 20 mg; L-H group, memantine 10 mg-memantine 20 mg; H-H group, memantine 20 mg-memantine 20 mg

Figure 8. Changes in the SIB-J score over time in a Japanese long-term study (OC)



P-H group, placebo-memantine 20 mg; L-H group, memantine 10 mg-memantine 20 mg; H-H group, memantine 20 mg-memantine 20 mg

Figure 9. Changes in the ADCS ADL-J score over time in a Japanese long-term study (OC)

The time course shows that the SIB-J score became higher in the H-H group than in the other groups at Week 52, and that the symptom progression became slower in the P-H group after 24 weeks of treatment with memantine. The rate of deterioration was considered slower in the memantine groups during long-term treatment than in the placebo group during the double-blind phase. Also in Study MRZ90001-9605, the score was better in the M-M group than in the P-M group, similar to the results of the Japanese study.

The time course of ADCS ADL-J scores shows that the rate of deterioration in the open-label extension phase was slower in the P-H group than in other groups. The rate of deterioration was considered slower in the memantine groups during the long-term treatment than in the placebo group during the double-blind phase.

The results of the Japanese long-term study suggest that long-term treatment with memantine is effective.

PMDA considers as follows:
The Japanese long-term study was an open-label non-controlled study, and therefore, had limitations in evaluating the long-term efficacy of memantine. Nevertheless, PMDA has concluded that the above study results suggest the effects of memantine to control symptoms of AD. Since the progression of AD cannot be completely controlled by treatment with memantine, a caution against injudicious use of memantine in non-responding patients should be included in the package insert.

4.(iii).B.(3) Safety

4.(iii).B.(3).1) Time of onset of adverse events

The applicant explained the safety of memantine for each treatment period as follows:
In Japanese double-blind comparative studies (Studies IE2101 [double-blind phase], IE2201, IE3501, and MA3301), the incidence of adverse events by time to the first onset (time from the start of treatment to the first onset of an adverse event) in the placebo group and the memantine 20 mg group was as follows: <4 weeks, 23.2% (120 of 517 subjects) and 25.8% (214 of 829 subjects), respectively; ≥4 to <8 weeks, 18.5% (93 of 502 subjects) and 16.4% (132 of 806 subjects), respectively; ≥8 to <12 weeks, 10.3% (50 of 484 subjects) and 12.8% (100 of 780 subjects), respectively; and ≥12 weeks, 29.1% (136 of 468 subjects) and 26.4% (202 of 765 subjects), respectively. These results showed no significant differences between the placebo and memantine 20 mg groups in any time segment, and suggested that there was no relationship between the incidence and time to the first onset in the memantine 20 mg group. Meanwhile, the incidence of adverse drug reactions by time to the first onset in the placebo group and the memantine 20 mg group was as follows: <4 weeks, 5.6% (29 of 517 subjects) and 9.4% (78 of 829 subjects), respectively; ≥4 to <8 weeks, 5.2% (26 of 502 subjects) and 4.8% (39 of 806 subjects), respectively; ≥8 to <12 weeks, 5.0% (24 of 484 subjects) and 3.8% (30 of 780 subjects), respectively; and ≥12 weeks, 14.3% (67 of 468 subjects) and 14.8% (113 of 765 subjects), respectively. A significant intergroup difference was detected in the subgroup with the time to the first occurrence being <4 weeks ($P = 0.0122$, χ^2 test). In this subgroup, among subjects receiving 20 mg of memantine, dizziness had the highest incidence (2.1%; 17 of 829 subjects), while other adverse events occurred in <1% of subjects. Therefore, patients should be carefully monitored for dizziness at an early stage of treatment (dose-titration phase).

The safety of long-term treatment with memantine was investigated by a stratified analysis of the Japanese subjects included in the safety analysis set (consisting of subjects who received at least one dose of memantine in any of the double-blind comparative studies or open-label studies), in which subjects were divided into 5 subgroups based on the following time segments to the first onset of adverse events; ≤6 months, >6 months to ≤1 year, >1 to ≤2 years, >2 to ≤3 years, and >3 years. The results of the analysis showed no upward trends in the incidence of adverse events as treatment duration increased. None of the relatively common adverse events were newly reported in any of >1 year segments.

PMDA considers as follows:
The applicant's explanation is appropriate in terms of the need for a precaution regarding dizziness, which occurred frequently in the early stage of memantine treatment. There is no particular safety concern in administering memantine at a dose titrated from 5 mg in weekly increments of 5 mg provided the patient's condition is carefully monitored during the early stage of treatment and during the dose-titration period.

4.(iii).B.(3).2) Dizziness

PMDA asked the applicant to explain the appropriateness of the precaution regarding dizziness, taking into consideration risk factors and the incidence of adverse events associated with dizziness such as fall and fracture.

The applicant explained as follows:
In the memantine 20 mg groups in Japanese double-blind comparative studies and the 3 main foreign studies, dizziness occurred in 19 of 521 subjects and 22 of 506 subjects, respectively. Of these subjects, 13 subjects in Japanese double-blind comparative studies and 10 subjects the 3 main foreign studies experienced the event during the dose-titration phase at an early stage of treatment, and study treatment was discontinued in 6 subjects and 1 subject, respectively, of these subjects. Among the subjects who experienced dizziness, 2 of the 19 subjects in the Japanese double-blind comparative studies were reported to have femur fracture (occurring on the same day as dizziness in 1 subject), and 2 of the 22 subjects in the 3 main foreign studies were reported to experience fall (occurring on the same day as dizziness in both subjects). Although the number of subjects withdrawn from the study due to dizziness was larger in Japanese studies than in foreign studies, most of the cases were mild to moderate in severity. In addition, there were no notable differences in the incidence of dizziness or fracture/fall associated with dizziness between Japanese and foreign studies, and subjects who experienced dizziness had no specific risk factors other than being at an early stage of treatment. Therefore, it is considered appropriate to include the following statement in the "Important Precautions" section of the draft package insert: "Dizziness may occur during the early stage of treatment with memantine. Patients should be closely monitored at this time, and if any abnormality is detected, appropriate measures should be taken such as discontinuation of treatment."

PMDA considers that the precaution regarding dizziness is appropriate at present, and that collection of information about the risk for dizziness and associated fall and fracture should be continued after the market launch.

4.(iii).B.(3).3) Adverse events in patients with renal impairment

PMDA asked the applicant to explain the reasons why the results of a subgroup analysis of Japanese double-blind comparative studies revealed that the incidence of falls reported as an adverse event was higher in subjects with concurrent renal impairment (18.0% [11 of 61 subjects]) than in subjects without concurrent renal impairment (7.0% [54 of 768 subjects]) in the memantine 20 mg group, but that it

showed no marked difference between the subjects with and without concurrent renal impairment (10.0% [4 of 40 subjects] and 9.0% [43 of 477 subjects], respectively) in the placebo group.

The applicant explained as follows:
Given that the pharmacokinetics of memantine is affected by the level of renal function, the incidence of adverse events was analyzed in subgroups stratified according to steady-state plasma memantine concentrations (in increments of 50 ng/mL), but no relationship was detected between the plasma concentration and the incidence of falls [see "4.(ii).B.(1) Effects of pharmacokinetic differences between Japanese and foreign populations"]. In an analysis in subgroups stratified by age: ≥50 and <65 years; ≥65 and <75 years; ≥75 and <85 years; and ≥85 years, the incidence of falls was found to increase with age in both the placebo and memantine 20 mg groups, and the incidence of falls tended to be high in subjects with a low body weight or with any concurrent disease in both groups.

While the incidence of falls reported as an adverse event was high in subjects with concurrent renal impairment in the memantine 20 mg group, the incidence of falls reported as an adverse drug reaction in the placebo group and the memantine 20 mg group was 2.5% (1 of 40 subjects) and 1.6% (1 of 61 subjects), respectively, in subjects with concurrent renal impairment, and 1.3% (6 of 477 subjects) and 1.2% (9 of 768 subjects), respectively, in subjects without concurrent renal impairment, with no obvious difference between those with and without concurrent renal impairment. Attending physicians considered individual cases of falls reported as adverse events to be incidental events associated with such factors as advanced age, underlying diseases, or complications, and a causal relationship of memantine to the events was ruled out in 16 of the 17 subjects with concurrent renal impairment.

These results suggested that a fall is an event resulting from risk factors such as age-related muscle weakness, a reduced body weight, and concurrent diseases, and that the higher incidence of falls in subjects with concurrent renal impairment than in subjects without concurrent renal impairment in the memantine 20 mg group was not directly attributable to renal impairment, but rather due to advanced age or other age-related risk factors.

PMDA considers as follows:
Taking into account that renal impairment is unlikely to be a direct risk factor for fall, and that the draft package insert recommends careful administration to patients with renal impairment, at present, no additional caution statement for patients with renal impairment is necessary. However, the collection of safety information in this patient population should be continued after market launch.

4.(iii).B.(3).4) Use in patients with hepatic impairment

PMDA pointed out the fact that the label of memantine in Europe includes the statement "Administration of memantine is not recommended in patients with severe hepatic impairment" and the label in the US states that "Memantine should be administered with caution to patients with severe hepatic impairment as the pharmacokinetics of memantine have not been evaluated in that population," and asked the

applicant whether or not a similar caution statement needs to be provided in Japan.

The applicant explained as follows:
Although a foreign clinical pharmacological study (Study MEM-PK-15) suggested that moderate hepatic impairment has no effects on the pharmacokinetics of memantine [see "4.(ii).A.(5).2) Pharmacokinetic study in foreign patients with hepatic impairment"], the above precautions are provided in the labels in Europe and the US because patients with severe hepatic impairment were not included in the above study, and therefore, no relevant data are available. In Japan, no data are available on patients with severe hepatic impairment treated with memantine because patients with an AST or ALT level of ≥2.5-fold the upper limit of normal range were excluded from clinical studies. However, pharmacokinetic factors and their effects on memantine were investigated in a PPK analysis on the data from a Japanese phase III study (Study MA3301), and the results suggest that hepatic function parameters (total bilirubin, AST [GOT], ALT [GPT], ALP, and γ-GTP) are unlikely to be significant factors affecting CL/F. Given that memantine is not readily metabolized, and is mostly excreted by the kidney as unchanged memantine, and that toxicity studies showed no toxic changes in the liver or its function, no safety risks have been clearly suggested in any of the Japanese studies. However, taking account of the unavailability of data in Japan, as in foreign countries, on the use of memantine in patients with severe hepatic impairment and the precautions provided in the labels in Europe and the US, "patients with severe hepatic impairment" will be included in the "Careful Administration" section of the package insert.

PMDA considers as follows:
The safety of memantine in patients with severe hepatic impairment is uncertain due to the lack of experience in this patient population in and outside Japan. However, given that hepatic impairment is unlikely to have any clinically relevant effect on the pharmacokinetics of memantine, its use in patients with severe hepatic impairment should not be contraindicated, and listing in the "Careful Administration" section is sufficient.

4.(iii).B.(4) Indication

The proposed indication of memantine is "Control of the progression of dementia symptoms in patients with moderate to severe Alzheimer's disease." The applicant provided the following justifications for the proposed severity level (moderate to severe). When memantine was first approved in Europe for the indication of AD, the review of memantine was mainly conducted based on Studies MRZ90001-9403 and MRZ90001-9605 (double-blind phase), and the severity level of the indicated illness was "moderately severe to severe Alzheimer's disease." In the US, memantine was reviewed based on the clinical data package consisting of the European clinical data package and additional data from Study MEM-MD-02, and was approved for the indication of "moderate to severe Alzheimer's disease." Subsequently, also in Europe, the indication of memantine was modified to "moderate to severe Alzheimer's disease" based primarily on the results from Study MRZ90001-9605 (double-blind phase) and from Study MEM-MD-01 that enrolled patients with AD in the same severity range as in Study

MEM-MD-02.

The Japanese early phase II study (Study IE2901) and the 2 main Japanese studies enrolled patients with AD in the same severity level as in the 3 main foreign studies: “moderately severe to severe Alzheimer’s disease” or “moderate to severe Alzheimer’s disease.” When Study IE2901 was started, it was planned to define the severity level of the study population as “moderately severe to severe Alzheimer’s disease” (i.e., a literal translation into Japanese). However, this tentative definition became controversial because the expression “moderately severe” had the potential to cause confusion in the conduct of the study. In the absence of any suitable alternative term, the word “severe” was selected for the study. Also in the subsequent 2 main Japanese studies, the patient population was specified as “patients with severe Alzheimer’s disease.” However, in addition to the circumstances behind the selection of the severity level in the above-mentioned clinical studies, given the similarity of study populations between the major Japanese and foreign clinical studies used for efficacy evaluation (Table 12), and to maintain terminological consistency with the US and Europe, the level of severity in patients for whom memantine is indicated in Japan is also proposed to be “moderate to severe Alzheimer’s disease.”

Table 12. Target patients in Japanese and foreign clinical studies

	IE2101 (Double-blind phase)	IE3501	MRZ900001-9605 (Double-blind phase)	MEM-MD-02	MEM-MD-01
Severity in target patients	Severe AD MMSE score, 5-14 FAST stage, 6a-7a		Moderately severe to severe AD MMSE score, 3-14 FAST stage, ≥ 6a GDS stage, 5-6	Moderate to severe AD MMSE score, 5-14	

Given that the inclusion criteria concerning the severity of AD were similar between Japanese and foreign clinical studies, and that memantine has not been investigated for the indication of controlling the progression of AD itself, PMDA considers that it is appropriate to propose the indication of memantine as follows: “Control of the progression of dementia symptoms in patients with moderate to severe Alzheimer’s disease.”

4.(iii).B.(5) Dosage and administration

The “DOSAGE AND ADMINISTRATION” section of the draft package insert includes the statement that “The dose may be reduced according to the patient’s condition,” which indicates the possibility of continuous administration of memantine at a maintenance dose lower than 20 mg. With regard to this statement, PMDA asked the applicant to explain whether or not it is appropriate to allow continuous administration of memantine at a reduced maintenance dose as needed, despite the facts that the efficacy of memantine at 10 mg was not demonstrated in terms of either of the 2 primary endpoints in Study IE2101 (double-blind phase), and that the efficacy of memantine was not investigated in Study IE3501 at any dose levels other than 20 mg.

The applicant explained as follows:

Dose reduction may be required in patients with potential risk factors for elevation of plasma memantine

concentration, such as low body weight, severe renal impairment, or high urine pH. Given that AD is a progressive disease and that the continuation of its treatment is considered necessary under careful clinical monitoring even when administration of memantine at a maintenance dose of 20 mg is not feasible due to adverse events, dose reduction has been specified in the propose dose and administration. Furthermore, in patients with severe renal impairment, steady-state plasma memantine concentrations after dose reduction to 10 mg were estimated to be within the range of mean plasma memantine concentrations following administration of meantime at 20 mg as shown in Study IE3501 [see "4.(ii).B.(4) Dosage and administration in patients with severe renal impairment"]. Meanwhile, injudicious use of memantine should be avoided in non-responding patients. Therefore, the following caution statement is provided in the "Important Precautions" section of the draft package insert: "This drug should not be administered without careful consideration when the patient does not respond to the treatment."

PMDA considers the dosage and administration of memantine as follows:
As stated above, there is a remaining issue, i.e., the 2 main Japanese studies failed to demonstrate the efficacy of memantine in terms of CIBIC plus-J scores. However, given that the efficacy has been shown at 20 mg in terms of SIB-J scores, one of the primary endpoints, if a final decision is made to approve memantine, 20 mg is considered to be an appropriate maintenance dose. The proposed dosage regimen at an early stage of treatment specifies that memantine is started at 5 mg once daily and titrated upward in weekly increments of 5 mg, which is considered appropriate because there was no marked difference in the incidence of adverse events between the memantine group and the placebo group during the dose-titration phase in the 2 main Japanese studies, and because adverse drug reactions such as dizziness occurred at an early stage of treatment, as stated in Section 4.(iii).B.(3).1). Therefore, it is acceptable to include the following statement in the "DOSAGE AND ADMINISTRATION" section in the draft package insert: "The usual adult starting dose of memantine hydrochloride is 5 mg once daily orally. The dose should be titrated in weekly increments of 5 mg to the maintenance dose of 20 mg once daily." The applicant's rationale for dose reduction according to the patient's condition is reasonable because based on the results of Study IE1601, memantine exposure is expected to be similar between patients with severe renal impairment treated at a maintenance dose of 10 mg and patients with normal renal function treated at a maintenance dose of 20 mg. However, the statement "The dose may be reduced according to the patient's condition." is inappropriate for the following reasons: (1) this dose reduction should be explained in the "Precautions for Dosage and Administration" section; (2) the extent of an increase in plasma memantine concentrations is uncertain when 20 mg of memantine is administered to patients with a low body weight or high urine pH compared with patients with no such factors; and (3) it is inappropriate to continue treatment at 10 mg, a dose level with unproven efficacy, in patients for whom the maintenance dose of 20 mg is not feasible due to adverse events.

A final decision on the dosage and administration of memantine will be made, taking account of comments from the Expert Discussion.

4.(iii).B.(6) Post-marketing surveillance etc.

The applicant provided the following explanations for post-marketing surveillance etc.:

Memantine is a renally excreted drug, and in the Japanese draft package insert, patients with renal impairment are included in the "Careful Administration" section, and precautions for patients with severe renal impairment, including dose reduction to 10 mg, are provided in the "Precautions for Dosage and Administration" section. In line with the labels in the US and Europe, patients with severe hepatic impairment will be included in the "Careful Administration" section of the Japanese package insert. Based on the above, information on the use results in patients with renal or hepatic impairment will be collected, and the safety of memantine in these populations will be investigated in a use-results survey. The planned number of patients in the use-results survey is 2500 patients on the basis of the proportions of target survey populations with renal or hepatic impairment and the incidence of adverse drug reactions reported from these populations in clinical studies during development. Information on any use in pregnant, parturient, or breast-feeding women will also be collected to identify clinical concerns in these populations, and patients treated with memantine will be followed up whenever possible.

PMDA considers that, in addition to the safety information on memantine use in patients with hepatic or renal impairment, information should also be collected in the post-marketing surveillance setting on the safety and efficacy in long-term use, concomitant use with donepezil, or use as a replacement drug for donepezil. A final decision on the details of post-marketing surveillance etc. will be made, taking account of comments from the Expert Discussion.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

A document-based inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, there were no particular problems. Thus, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted product application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection took place in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.1.1, 5.3.5.1.2, 5.3.5.2.2, 5.3.5.2.4, and 5.3.5.4.1). As a result, the following findings were noted at some clinical trial sites: insufficient IRB review record, protocol deviations (the use of prohibited concomitant medications), inappropriate record retention, and others. However, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

IV. Overall Evaluation

Based on the submitted data from Japanese clinical studies, the superiority of 20 mg of memantine over

placebo has been demonstrated with reproducibility in terms of SIB-J scores, a cognitive function endpoint, but not in terms of CIBC plus-J or ADCS ADL-J scores as the endpoints representing overall clinical status or activities of daily living. Therefore, it is rather inconclusive whether or not the efficacy of memantine has been clearly demonstrated in Japanese patients with AD. However, it is of significance to provide memantine to clinical practice for the following reasons: (1) its efficacy has been demonstrated in foreign clinical studies evaluating cognitive function and overall clinical status or activities of daily living, and the product has already been used as a standard treatment in foreign countries; (2) its superiority over placebo in terms of SIB-J scores has been demonstrated in Japanese clinical studies; (3) it has a potential to become a new AD-treatment option due to its mechanism of action that is distinct from that of donepezil, which is the existing treatment option; and (4) there is a significant medical need for AD treatment in Japan. Nevertheless, the efficacy of memantine and its acceptability for marketing approval will be further reviewed, taking account of comments from the Expert Discussion. Further investigation will be needed in the post-marketing surveillance to make up for the paucity of information from clinical studies in the following areas: the safety of memantine in patients with renal or hepatic impairment; the safety and efficacy of memantine in long-term use; and the safety and efficacy of memantine used concomitantly with donepezil, or used as a replacement drug for donepezil.

Memantine may be approved if it is concluded based on comments from the Expert Discussion that this drug product can be expected to be effective in Japanese patients with AD.

Review Report (2)

November 12, 2010

I. Product Submitted for Registration

[Brand name]	Memary Tablets 5 mg, 10 mg, and 20 mg
[Non-proprietary name]	Memantine Hydrochloride
[Applicant]	Asubio Pharma Co., Ltd. (Currently Daiichi Sankyo Company, Limited)
[Date of application]	February 5, 2010

II. Content of the Review

The outline of the comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) is described in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations etc., concerning the product submitted for registration, 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).

1. Clinical positioning

PMDA has concluded that the applicant's viewpoint, outlined as follows, is acceptable: Although donepezil is the only drug currently marketed in Japan for the treatment of AD, the clinical positioning of memantine is considered not to differ significantly between in Japan and in foreign countries. Given that its mechanism of action is distinct from that of donepezil, which is the existing treatment option, memantine is believed to offer a new treatment option for patients with moderate to severe AD, and to thereby extend the treatment spectrum for the disease.
PMDA's conclusion mentioned above was supported by the expert advisors.

Furthermore, the expert advisors generally supported PMDA's conclusion that the efficacy and safety of memantine in combination with donepezil are expected to be clarified through the accumulation of clinical experience in Japan, and that the applicant should therefore actively collect and provide relevant information, and additionally made the following comments:

- In consideration that memantine is most likely to be used in combination with donepezil, and that the data from the US clinical study in patients with AD receiving donepezil (Study MEM-MD-02) cannot be extrapolated to the Japanese population, a clinical study in Japanese patients with AD is needed to verify the superior efficacy of memantine in combination with donepezil over memantine alone; and
- The efficacy of memantine has not yet been conclusively demonstrated, and therefore, a post-marketing clinical study should be conducted to investigate the efficacy of memantine in combination with donepezil [see "7. Post-marketing surveillance etc."].

2. Efficacy

The 2 main Japanese studies showed a significant difference in terms of cognitive function (SIB-J) between the memantine 20 mg group and the placebo group, but failed to demonstrate the superiority of memantine over placebo in terms of overall clinical status (CIBIC plus-J) and activities of daily living (ADCS ADL-J). The expert advisors made the following comments concerning the above results:

- Although changes in the various scores give an impression of improvement in comparison with the placebo group, the lack of statistically significant differences can be interpreted as indicating an extremely limited efficacy of memantine, and therefore, its efficacy has not yet been conclusively demonstrated;
- On the other hand, in patients with a disease that progresses very slowly such as AD, it is difficult to demonstrate the superiority of a drug over placebo in terms of clinical status or activities of daily living; and
- It is important to give due consideration to the need to address the current situation in which treatment options for AD are limited in Japan.

All of the expert advisors supported PMDA's conclusions that the current status of clinical practice in Japan should be taken into account, and that based on the results of Japanese and foreign clinical studies, the drug product can also be expected to be effective in Japanese patients with AD.

Concerning the applicant's explanation attributing the failure in demonstrating the efficacy of memantine in terms of CIBIC plus-J scores to the effects of outpatient care and rehabilitation services on the CIBIC plus-J evaluation, the expert advisors made the following comments:

- In Table 9 in Review Report (1), a comparison of the memantine group with the placebo group shows improvement in the subgroup not receiving outpatient care or rehabilitation services, but shows deterioration in the subgroup receiving these services. These results are difficult to interpret, and therefore, the applicant's explanation is not acceptable;
- It is still unclear whether or not the effects of outpatient care and rehabilitation services alone were responsible; and
- PMDA made a reasonable contention that efficacy in terms of cognitive function and activities of daily living or overall clinical status has to be demonstrated in the development of an anti-AD drug. However, the causal factors explaining why CIBIC plus-J scores did not demonstrate the efficacy of memantine should be further explored, and endpoints suitable for evaluation of Japanese patients with AD should be sought in collaboration with relevant academic societies from the perspective of promoting the future development of anti-AD drugs in Japan.

3. Safety

(1) Use of memantine in patients with renal impairment

The expert advisors supported PMDA's conclusion that although patients with renal impairment should be listed in the "Careful Administration" section of the package insert, this patient population is unlikely to require adjustment of the dosage regimen of memantine; this conclusion was based on the following explanation given by the applicant: Although the AUC_{∞} in Japanese patients with moderate renal

impairment increased to approximately 2-fold that seen in individuals with normal renal function, patients with moderate renal impairment enrolled in Japanese double-blind comparative studies experienced no major problems even without any dose adjustment, and no marked difference in the incidence of adverse events was observed in association with the difference in plasma memantine concentration when it was <250 ng/mL (equivalent to ≥2-fold the plasma concentration in individuals with normal renal function after a dose of 20 mg of memantine).

The expert advisors also supported PMDA's conclusion that based on the following efficacy and safety considerations, it is appropriate to select a maintenance dose of 10 mg, the same dose level as in foreign countries, for patients with severe renal impairment.

(i) The applicant's following explanation is acceptable:
No data are available for the efficacy of memantine at 10 mg in patients with severe renal impairment. However, based on the results of a pharmacokinetic study in Japanese patients with renal impairment (Study IE1601), memantine exposure in patients with severe renal impairment at a maintenance dose of 10 mg can be expected to be comparable to that in those with normal renal function at a maintenance dose of 20 mg; and

(ii) Although the number of study subjects was small, the incidence of adverse events was similar between the memantine 20 mg group and the placebo group in a Japanese double-blind comparative study.

Concerning the caution statement that "at a reduced maintenance dose of, for example, 10 mg once daily," proposed by the applicant for patients with severe renal impairment, the expert advisors commented that, given that the safety of memantine has not been sufficiently investigated in this patient population, the caution statement should be revised to "the maintenance dose in patients with severe renal impairment should be 10 mg once daily."

Based on the above, PMDA instructed the applicant to modify the caution statement for patients with severe renal impairment. The applicant followed this instruction.

(2) Use of memantine in patients with hepatic impairment

The expert advisors supported PMDA's following conclusions:

The safety of memantine in patients with severe hepatic impairment is uncertain due to the lack of experience in this population in and outside Japan. However, given that hepatic impairment is unlikely to have any clinically relevant effect on the pharmacokinetics of memantine, its use in patients with severe hepatic impairment need not be contraindicated, and listing in the "Careful Administration" section is appropriate.

4. Indication

A discussion was held on PMDA's conclusion that "Control of the progression of dementia symptoms in patients with moderate to severe Alzheimer's disease" is an appropriate indication for memantine because the inclusion criteria concerning the severity of AD were similar between the Japanese and

foreign clinical studies, and this drug substance has not been investigated as a treatment to control the progression of AD itself. Then the expert advisors made the following comments:

- It is appropriate for PMDA to accept the wording of "patients with moderate to severe Alzheimer's disease" as the target patients in the light of the terminological consistency with the US and Europe.
- However, the expression "control of the progression of dementia symptoms" can be misunderstood as control of the disease itself because the word "(to) control" implies "(to) stop." Therefore, the description of the indication may need to be revised to avoid potential misunderstandings.
- Given that memantine can only alleviate symptoms for a limited period of time, the above indication may raise unfounded expectations in patients and their family members.
- The description may also need to be changed to clearly distinguish memantine from anti-AD drugs intended for disease-modifying therapy currently under development.

The expert advisors concluded unanimously that, given that donepezil has been approved for the same indication, the proposed indication of memantine need not to be modified at present, but possible misunderstandings about its expected benefits should be avoided by raising the awareness of those involved in clinical practice, and the description of the indication, including the use of donepezil, should be further reviewed in the future.

The expert advisors supported PMDA's proposal that the following information be included in the "Precautions for Indication" section:

(i) Memantine should be used only in patients diagnosed with AD;
(ii) No data are currently available on the effects of memantine to control the progression of AD itself; and
(iii) Memantine has no confirmed efficacy for forms of dementia other than AD.

Furthermore, the expert advisors commented that it may be desirable to provide certain indicators that clearly define the severity level of "moderate to severe" AD and to caution against use in patients with mild AD.

In response to the above comment, PMDA proposed, for the following reasons, that the applicant be instructed to describe the key inclusion criteria for clinical studies in the "Clinical Studies" section of the package insert and in other information materials, and to thereby provide relevant information appropriately to those involved in clinical practice: There were minor differences in the inclusion criteria between Japanese and foreign clinical studies of memantine. The definitions of moderate to severe AD vary even among clinical studies of anti-AD drugs under development. Therefore, it is important to inform those involved in clinical practice of the characteristics of patients enrolled in clinical studies of memantine although the definitions of mild, moderate, and severe AD are currently not clear enough to be included in package inserts.

PMDA's proposal was supported by the expert advisors.

Based on the above, PMDA instructed the applicant to provide a relevant caution statement by creating a section of "Precautions for Indication", and appropriately inform those involved in clinical practice of the main inclusion criteria (e.g., MMSE, FAST) used in Japanese and foreign clinical studies as a reference for the AD severity levels. The applicant followed these instructions.

Although the proposed indication ("Control of the progression of dementia symptoms in patients with moderate to severe Alzheimer's disease") was concluded to be appropriate in the Expert Discussion, the applicant proposed that the description be revised with reference to the indication (at the initial approval) of an already approved drug of the same class. PMDA has concluded that the following indication is appropriate:

[Indication]
Control of the progression of dementia symptoms in patients with moderate to severe Alzheimer's disease

5. Dosage and administration

The expert advisors supported PMDA's conclusion that it is appropriate to select, based on the results of the 2 main Japanese studies, a maintenance dose of 20 mg once daily, a starting dose of 5 mg once daily, and subsequent titration in weekly increments of 5 mg, and that the following statement in the "DOSAGE AND ADMINISTRATION" section is acceptable: "The starting dose of memantine hydrochloride is 5 mg once daily orally. The dose should be titrated in weekly increments of 5 mg to the maintenance dose of 20 mg once daily."

A comment was made that the dose-titration interval could be more flexible, for example in increments of 5 mg every 1 or 2 weeks. PMDA responded with the following explanation: Although PMDA would not prohibit physicians from extending the interval beyond 1 week at their discretion, the interval of 1 week reflects the dosage and administration evaluated in clinical studies, and is therefore considered to be justified as the dose-titration interval for the approved dosage and administration.

The expert advisors also supported PMDA's conclusion that the statement "The dose may be reduced according to the patient's condition" was inappropriate for the following reasons:

(i) This precautionary statement on dose reduction should be explained in the "Precautions for Dosage and Administration" section, although patients with severe renal impairment require dose reduction to 10 mg.
(ii) It is unclear to what extent plasma memantine concentrations are increased following the administration of 20 mg of memantine to patients with a low body weight or high urine pH, which were listed by the applicant as factors warranting dose reduction, compared with patients with no such factors.
(iii) It is inappropriate to continue treatment at 10 mg, a dose level with unproven efficacy, in patients for whom the maintenance dose of 20 mg is not feasible due to adverse events.

Based on the above, PMDA has concluded that the descriptions of the "Dosage and Administration" and "Precautions for Dosage and Administration" should be revised as follows:

[Dosage and administration]
The usual adult starting dose of memantine hydrochloride is 5 mg once daily orally. The dose should be titrated in weekly increments of 5 mg to the maintenance dose of 20 mg once daily.

[Precautions for Dosage and Administration]
(1) Titration from the starting dose of 5 mg once daily is intended to prevent the occurrence of adverse drug reactions, and therefore, should be continued until the maintenance dose is reached.
(2) Memantine should be carefully administered to patients with severe renal impairment (creatinine clearance of <30 mL/min) at a maintenance dose of 10 mg once daily while monitoring the patient's condition (see the "Careful Administration" and "Pharmacokinetics" sections).
(3) Memantine should be administered under the supervision of a healthcare professional, a family member, etc.

6. Discontinuation of treatment with memantine
The expert advisors made the following comments:
- Given the prevalence in clinical practice of non-compliance with precautions against injudicious use of the approved anti-AD drug in non-responding patients, enforceable restrictions (such as criteria for long-term use) may be necessary.
- The indication described as "control of the progression" may mislead healthcare professionals into believing that memantine prevents the progression of AD, resulting in unbeneficial long-term use.
- The "INDICATION" section should include the following statement to prevent unlimited use in clinical practice: "It is unclear how long the efficacy is maintained in patients treated with memantine for several years."

The following comment was also made: Whether or not to discontinue anti-AD treatment is at the discretion of prescribing physicians, and relevant academic societies etc., should also discuss what measures should be taken to address this issue.

PMDA explained as follows:
Anti-AD treatment cannot be discontinued without a consensus being reached between the physician and the patient's family members and caregivers. Given that inclusion of discontinuation criteria in the package insert may hinder flexible, individualized treatment, it is difficult to include specific restrictions or criteria in the package insert. Nevertheless, it is important to provide relevant information to those involved in clinical practice, and PMDA would like to instruct the applicant to promote awareness among those involved in clinical practice through the provision of information materials and others.

In the light of the above, PMDA requested the applicant to consider measures to raise awareness among those involved in clinical practice to ensure that the injudicious use of memantine is prevented when it

becomes obvious that this product can no longer be expected to be effective due to progression of AD. The applicant responded that, in collaboration with medical experts, the applicant would ensure that physicians and pharmacists understand the properties of memantine, by widely disseminating relevant information to those involved in clinical practice, such as the Summary of Pharmaceutical Product Information and the Interview Form, and by accurately explaining the precautions and the information on proper use. PMDA considered that the proposed countermeasures were generally appropriate, and accepted the applicant's response.

7. Post-marketing surveillance etc.

The expert advisors supported PMDA's conclusion that, in addition to the safety information on memantine use in patients with hepatic or renal impairment, information should also be collected in the post-marketing surveillance setting on the safety and efficacy of memantine in long-term use, and used concomitantly with donepezil, or used as a replacement drug for donepezil.

The expert advisors made the following comments:

- In order to maintain consistency with the methods used in the 2 main Japanese studies, the use of a cognitive function assessment scale (SIB-J) as an endpoint is desirable in the post-marketing surveillance;
- Commonly used evaluation scales, such as MMSE and Revised Hasegawa's Dementia Scale, are also appropriate as endpoints; and
- Since memantine is likely to be used in combination with donepezil in clinical settings, its efficacy and safety in combination with donepezil should be investigated in a post-marketing clinical study [see "1. Clinical positioning"].

The expert advisors concluded by agreeing on the need for a post-marketing clinical study.

PMDA instructed the applicant to submit an outline of a post-marketing surveillance plan (draft) designed to enable the collection of the above information, also taking account of the feasibility of such surveillance in clinical practice. The applicant submitted a draft protocol of a use-results survey, and responded that information would be collected in accordance with PMDA's instructions. The applicant also responded that they would conduct a post-marketing clinical study to investigate the efficacy and safety of memantine in patients receiving donepezil.

PMDA has concluded that, although the details of the plan including protocols of the post-marketing clinical study and use-results survey should be closely reviewed in the future, the submitted outline of the post-marketing surveillance plan (draft) was generally appropriate, and accepted the applicant's response.

III. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after the

indication and the dosage and administration are modified as shown below. It is appropriate to set the re-examination period at 8 years. The drug substance and the drug product are both classified as powerful drugs. The product is not classified as a biological product or a specified biological product.

[Indication]	Control of the progression of dementia symptoms in patients with moderate or severe Alzheimer's disease
[Dosage and administration]	The usual adult starting dose of memantine hydrochloride is 5 mg once daily orally. The dose should be titrated in weekly increments of 5 mg to the maintenance dose of 20 mg once daily.