Report on the Deliberation Results

September 3, 2024

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

Brand Name	Rozebalamin for Injection 25 mg
Non-proprietary Name	Mecobalamin (JAN*)
Applicant	Eisai Co., Ltd.
Date of Application	January 26, 2024

Results of Deliberation

In its meeting held on August 26, 2024, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 10 years. The drug product is not classified as a poisonous drug or a powerful drug.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Review Report

August 8, 2024
Pharmaceuticals and Medical Devices Agency

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

Brand Name Rozebalamin for Injection 25 mg
Non-proprietary Name Mecobalamin
Applicant Eisai Co., Ltd.
Date of Application January 26, 2024
Dosage Form/Strength
Lyophilized formulation for injection: Each vial contains 28.75 mg of mecobalamin.
Application Classification Prescription drug, (4) Drug with a new indication, (6) Drug with a new dosage, (8-2) Drug in an additional dosage form (not during the re-examination period)
Items Warranting Special Mention
Orphan drug (Orphan Drug Designation No. 542 of 2022 [*R4 yaku*]; PSEHB/PED Notification No. 0526-14 dated May 26, 2022, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)
Reviewing Office Office of New Drug III

Results of Review
On the basis of the data submitted, PMDA has concluded that the product has efficacy in slowing the progression of functional impairment in amyotrophic lateral sclerosis (ALS), and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following condition.

Indication
Slowing of the progression of functional impairment in patients with amyotrophic lateral sclerosis (ALS)

Dosage and Administration
The usual adult dosage is 50 mg of mecobalamin injected intramuscularly, once daily, twice weekly.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

June 26, 2024

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

Product Submitted for Approval

Brand Name	Rozebalamin for Injection 25 mg
Non-proprietary Name	Mecobalamin
Applicant	Eisai Co., Ltd.
Date of Application	January 26, 2024

Dosage Form/Strength

Lyophilized formulation for injection: Each vial contains 28.75 mg of mecobalamin.

Proposed Indication

Slowing of the progression of functional impairment in patients with amyotrophic lateral sclerosis (ALS)

Proposed Dosage and Administration

The usual adult dosage is 50 mg of mecobalamin injected intramuscularly, once daily, twice weekly.

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List of Abbreviations

See Appendix.

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

Amyotrophic lateral sclerosis (ALS) is a disease characterized by progressive degeneration of upper and lower motor neurons and has been designated as "designated intractable disease." Patients with the disease typically present with progressive generalized skeletal muscle weakness and atrophy. As ALS progresses, patients gradually lose their ability to perform activities of daily living, which may lead to pneumonia aspiration due to bulbar palsy or respiratory failure due to paralysis of the respiratory muscles. Although the median survival in patients without ventilatory support is expected to be 3 to 4 years, the progression of the symptoms and prognosis are variable among individual patients. The incidence of ALS peaks at the ages of 60 to 79, and the estimated annual prevalence of ALS in Japan is 9.9 per 100000 population (Practical Guideline for Amyotrophic Lateral Sclerosis 2023, Drafting Committee for Practical Guideline for Amyotrophic Lateral Sclerosis ed.).

Mecobalamin is an active form of vitamin B_{12}. In Japan, as the products containing the active substance mecobalamin, "Methycobal Injection 500 μg" for intramuscular/intravenous administration has been approved for the indications of "peripheral neuropathy" and "megaloblastic anemia caused by vitamin B_{12} deficiency," and "Methycobal Tablets 250 μg" etc.[1)] for oral administration have been approved for the indication of "peripheral neuropathy." Outside Japan, as of June 2024, the formulations containing the active substance mecobalamin have been approved for the indications of peripheral neuropathy and megaloblastic anemia caused by vitamin B_{12} deficiency in 30 countries or regions, but not for the indication of ALS in any country or region.

The clinical development of mecobalamin for ALS began in [redacted] 20[redacted]. The applicant has now filed a marketing application for the indication of ALS, based on the data from clinical studies including an investigator-initiated clinical study. A Japanese phase III study (CTD 5.3.5.1.2 and 5.3.5.1.3, Study E0302-TOK-763) was conducted as research projects of the MHLW and the Japan Agency for Medical Research and Development (AMED).[2)]

The proposed product received an orphan drug designation (Orphan Drug Designation No. 542 of 2022 [*R4 yaku*]; PSEHB/PED Notification No. 0526-14 dated May 26, 2022) with the intended indication of "slowing of the progression of the disease and functional impairment in patients with amyotrophic lateral sclerosis (ALS)."

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

The drug substance mecobalamin is listed in the Japanese Pharmacopoeia (JP), and the manufacturing process and site for mecobalamin are the same as those for the drug substance used in the currently approved product, "Methycobal Injection 500 μg." The proposed drug substance specification is the same as the specification for mecobalamin (JP), except for [redacted], and [redacted] has been included in the specification of the attachment.

1) Methycobal Tablets 250 μg, Methycobal Tablets 500 μg, and Methycobal Fine Granules 0.1%
2) A practical research project for rare/intractable diseases funded by the Japan Agency for Medical Research and Development (AMED) and a research project on rare/intractable diseases under the Health and Labour Sciences Research Grants

The long-term stability data have been submitted in the present application, and no significant changes in quality occurred. Thus, a retest period of [redacted] months has been proposed for the drug substance.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a lyophilized formulation for injection. Each vial contains 28.75 mg of mecobalamin and the following excipients: lactose hydrate, sodium dihydrogen phosphate dihydrate, and sodium hydroxide. An overage is used to ensure that 25 mg of mecobalamin can be withdrawn after reconstitution with 2.3 mL of saline.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of formulation, sterile filtration, filling, lyophilization, crimping, visual inspection and sorting, packaging/labeling, storage, and testing. [redacted], [redacted], [redacted], [redacted], and [redacted] have been defined as critical steps, and process control items and values have been established for these steps.

A quality control strategy was established based on the following etc. (Table 1).

- Identification of critical quality attributes (CQAs)
- Quality risk assessments

Table 1. Overview of drug product control strategy

CQA	Method of control
Sterility	Manufacturing process, Specification
Bacterial endotoxins	Manufacturing process, Specification
Strength	Manufacturing process, Specification
Related substances	Manufacturing process, Specification
Foreign insoluble matter	Manufacturing process, Specification
Insoluble particulate matter	Manufacturing process, Specification

2.2.3 Control of drug product

The proposed specifications for the drug product consist of strength, description, identification (high performance liquid chromatography [HPLC], ultraviolet-visible spectroscopy [UV/VIS]), osmotic pressure ratio, pH, purity [clarity and color of solution, related substances (HPLC)], bacterial endotoxins, uniformity of dosage units (mass variation test), foreign insoluble matter, insoluble particulate matter, sterility, reconstitution time, and assay (HPLC).

2.2.4 Stability of drug product

Table 2 shows the primary stability studies on the drug product. The stability results indicated that the drug product is stable. Photostability data showed that the drug product in its final container is photostable.

Table 2. Stability studies on drug product

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term	3 commercial-scale batches	25 ± 2°C	60 ± 5%RH	Glass vial + fluoropolymer laminated butyl rubber stopper + aluminum cap + vial bottom label + aluminum-deposited polyethylene terephthalate shrink film + carton	60 months
Accelerated		40 ± 2°C	75 ± 5%RH		6 months

Based on the above, a shelf-life of 60 months has been proposed for the drug product when filled in a glass vial closed with a fluoropolymer laminated butyl rubber stopper and an aluminum cap and then labeled (vial bottom label), packaged in an aluminum-deposited polyethylene terephthalate shrink film, and stored in a carton to protect from light at room temperature.

2.R Outline of the review conducted by PMDA

Based on the submitted data and the following considerations, PMDA concluded that the quality of the drug substance and the drug product is adequately controlled.

2.R.1 Novel excipients

The drug product contains a novel excipient, lactose hydrate in an amount higher than the amounts present in existing intramuscular formulations.

PMDA's conclusion:

Lactose hydrate contained in the drug product conforms to the JP, and there are no problems with the specification or stability. Based on the submitted data, there are no safety issues with lactose hydrate at the level used in the drug product for the present application.

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

The applicant submitted the results from primary pharmacodynamic and safety pharmacology studies as non-clinical pharmacology studies of mecobalamin. The results from the main studies are described below.

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies

3.1.1.1 Protection against oxidative stress in human induced pluripotent stem (iPS) cell-derived motor neurons (CTD 4.2.1.1.10)

Human iPS cell-derived motor neurons were cultured in an antioxidant-free medium, and the effects of mecobalamin (0.1, 0.3, or 1 μmol/L), edaravone (3, 10, or 30 μmol/L), or riluzole (0.1, 1, or 10 μmol/L) on neurite injury induced by oxidative stress in the medium were evaluated based on the time to the first observation of <50% of the maximum length of total neurite outgrowth per unit area (H50 value). Mecobalamin and edaravone increased the H50 value in a concentration-dependent manner, and riluzole increased the H50 value at 10 μmol/L.

3.1.1.2 Protection against neuronal death induced by Cu/Zn superoxide dismutase 1 (SOD1) (G93A)-expressing astrocytes in mouse embryonic stem (ES) cell-derived motor neurons (Reference data CTD 4.2.1.1.1)

Astrocytes prepared from the SOD1 (G93A) transgenic mouse (an animal model of ALS)[3)] (B6.Cg-Tg (SOD1-G93A)1Gur/J) and motor neurons differentiated from mouse ES cells were co-cultured with mecobalamin (1, 10, or 100 nmol/L) or vehicle (distilled water), and the protective effect of mecobalamin against neuronal death was evaluated. Mecobalamin increased the number of surviving cells at ≥10 nmol/L.

3.1.1.3 Protective effects in cultured retinal neurons and cultured cortical neurons (Reference data CTD 4.2.1.1.2 and 4.2.1.1.3: *Invest Ophthalmol Vis Sci.* 1997; 38: 848-54, *Eur J Pharmacol*. 1993; 241: 1-6)

The protective effects of mecobalamin (0.01, 0.1, 1, or 10 μmol/L) against glutamate-induced neurotoxicity in fetal rat retinal neurons or fetal rat cortical neurons were evaluated. Mecobalamin inhibited both neuronal deaths in a concentration-dependent manner.

Mecobalamin at 1 μmol/L inhibited the neurotoxicity induced by sodium nitroprusside in fetal rat retinal neurons. Furthermore, mecobalamin at 10 μmol/L inhibited the neurotoxicity induced by NMDA or sodium nitroprusside in fetal rat cortical neurons.

3.1.1.4 Effect on axonal outgrowth in cerebellar granule cells (Reference data CTD 4.2.1.1.4: *Exp Neurol*. 2010; 222: 191-203)

Using the axonal length in rat cerebellar granule cells as an index, cerebellar granule cells were cultured with mecobalamin (0.001-100 μmol/L), and mecobalamin promoted axonal outgrowth at ≥0.1 μmol/L.

3.1.1.5 Protection and rescue against homocysteine-induced cell death in NSC-34D cells (Reference data CTD 4.2.1.1.5: *Toxicol Appl Pharmacol*. 2011; 251: 217-25)

Using NSC-34D cells (the differentiated NSC-34 cell line [Mouse Motor Neuron-Like Hybrid Cell Line (motor neuron-neuroblastoma)]), the protective and rescue effects of mecobalamin against homocysteine-induced cell death were evaluated. Mecobalamin decreased cell death, and the IC_{50} values of mecobalamin for simultaneous exposure with homocysteine and pretreatment at 2 hours prior to homocysteine were 0.4 and 0.6 μmol/L, respectively.

3.1.2 *In vivo* studies

3.1.2.1 Effect on survival in mouse model of ALS (Reference data CTD 4.2.1.1.6)

Mecobalamin (10 mg/kg) was administered subcutaneously, riluzole (100 μg/mL) was administered freely in drinking water, or vehicle was administered (saline was administered subcutaneously or administered in drinking water) in an animal model of ALS, the SOD1 G93A transgenic mouse[3)] (B6SJL-Tg (SOD1-

3) SOD1 mutations account for approximately 20% of familial ALS cases, and the SOD1 G93A transgenic mouse is an animal model of ALS (*Neuroscience*. 2013; 246: 281–90).

G93A)1Gur/J) at 50 days of age. There was a trend towards prolonged/increased survival etc. in the mecobalamin and riluzole groups compared to the vehicle group.

3.1.2.2 Neuroprotective effect in mouse model of ALS (Reference data CTD 4.2.1.1.7: *J Neurol Sci*. 2015; 354: 70-4)

Wobbler mice (an animal model of ALS) (*Mol Genet Genomics*. 2013; 288: 207-29) received mecobalamin (3, 30 mg/kg) or vehicle by intraperitoneal administration for 4 weeks from the onset of tremor. Mecobalamin 30 mg/kg inhibited forelimb grip strength deficits, which are observed in the animal model, and increased the weight of the bicep muscles and the number of musculocutaneous nerves.

3.1.2.3 Regeneration of degenerating motor nerve terminals in the anterior gracile muscle of gracile axonal dystrophy (GAD) mouse (Reference data CTD 4.2.1.1.8: *Neurosci Lett*. 1994; 170: 195-7)

GAD mice received oral mecobalamin (1 mg/kg) or vehicle (saline) for 25 days. In the distal endplate zone of the muscle, motor nerve terminals were degenerated in both the mecobalamin and vehicle groups. On the other hand, in the proximal endplate zone, where few degenerated terminals were seen in both groups of the mice, the perimeter of the terminals was increased, and the area of the terminals was decreased in mecobalamin-treated mice compared to vehicle-treated mice.

3.1.2.4 Nerve regeneration in rat model of acrylamide neuropathy (Reference data CTD 4.2.1.1.9: *J Neurol Sci*. 1994; 122: 140-3)

Based on the amplitudes of compound muscle action potentials (CMAPs) after tibial nerve stimulation, the effects of mecobalamin (50, 500 μg/kg) or vehicle (saline) on the axonal regeneration in an acrylamide neuropathy model created by administering acrylamide to rats for 4 weeks were evaluated. Five doses of mecobalamin or vehicle were administered intraperitoneally per week for 12 to 13 weeks. Rats treated with mecobalamin 500 μg/kg showed faster recovery from decreased CMAP amplitudes induced by acrylamide than vehicle-treated rats.

3.2 Safety pharmacology

An overview of safety pharmacology studies is shown in Table 3.

Table 3. Overview of safety pharmacology studies

Organ systems evaluated	Test system	Endpoints/Method of assessment, etc.	Duration of dosing (Regimen)	Route of administration	Doses	Findings	CTD
CNS	Rat (6 males/group)	Functional observational battery (FOB)	Single dose	IM	0,[a] 4, 16 mg/kg	No effects	4.2.1.3.1
Cardiovascular	HEK293 cells	hERG current	*In vitro*		0,[b] 10 μmol/L	No effects	4.2.1.3.2
	Isolated guinea pig papillary muscles	Resting membrane potential, action potential amplitude, V_{max}, APD_{50}, APD_{90}	*In vitro*		0,[c] 10 μmol/L	No effects	4.2.1.3.3
	Dog (3/sex/group)	Blood pressure (systolic and diastolic blood pressures), heart rate, ECG (PQ interval, QRS duration, QT/QTc interval)	Single dose	IM	0,[a] 10 mg/kg	No effects	4.2.1.3.4
Respiratory	Dog (3/sex/group)	Respiratory rate and blood gas parameters (arterial blood pH, oxygen partial pressure, partial pressure of carbon dioxide, oxygen saturation)	Single dose	IM	0,[a] 10 mg/kg	No effects	4.2.1.3.4

V_{max}, maximal rate of rise; APD_{50}, action potential duration at 50% repolarization; APD_{90}, action potential duration at 90% repolarization
a) Vehicle: saline
b) Vehicle: 0.1% DMSO, 137 mmol/L NaCl, 4 mmol/L KCl, 1.8 mmol/L $CaCl_2$, 1.0 mmol/L $MgCl_2$, 10 mmol/L D-glucose, 10 mmol/L HEPES, pH7.4
c) Vehicle: Tyrode′s solution containing 0.1% DMSO

3.R Outline of the review conducted by PMDA

3.R.1 Primary pharmacodynamic studies of mecobalamin

The applicant's explanation about the effects of mecobalamin in ALS:

In the pathogenesis of ALS, excitatory amino acids, oxidative stress, etc., are thought to be involved in motor neuron death, but the exact ALS disease mechanisms are unknown (*Front Aging Neurosci*. 2017; 9: 68). Although the mechanism of action of mecobalamin in ALS is unclear, as the following findings etc. indicate that mecobalamin has neuroprotective effects, mecobalamin is expected to show efficacy in ALS.

- Mecobalamin has been reported to protect against oxidative stress-induced neurite injury [see Section 3.1.1.1], neuronal death induced by SOD1 (G93A)-expressing astrocytes [see Section 3.1.1.2], and excitatory neuronal death and to promote axonal outgrowth [see Section 3.1.1.3 to 3.1.1.5].
- Since the test conditions of a study in the SOD1 G93A transgenic mouse were different from those specified in the previous literature, etc., this test system may have been unsuitable for evaluating the survival benefit [see Section 3.1.2.1]. Meanwhile, mecobalamin has been reported to improve muscle weakness and motor neuron degeneration in Wobbler mice [see Section 3.1.2.2] and promote nerve regeneration in GAD mice or rats with acrylamide neuropathy [see Sections 3.1.2.3 and 3.1.2.4].

Homocysteine is involved in neurodegeneration, and patients with ALS have higher plasma homocysteine levels compared with healthy adults (*Neurology*. 2008; 70: 222-5, *Amyotroph Lateral Scler*. 2010; 11: 140-7, etc.). *S*-adenosylmethionine, synthesized from methionine, is involved in the repair of proteins damaged by oxidative stress (*Eur J Biochem*. 2000; 267: 4397-405). Thus, as a coenzyme of methionine synthase that catalyzes the conversion of homocysteine to methionine, mecobalamin is considered to act against ALS progression through its mechanisms of protection and rescue from homocysteine-induced cell death, repair of damaged proteins via *S*-adenosylmethionine, etc.

PMDA's view:

Although the mechanism of action of mecobalamin in ALS has not fully been elucidated, the applicant's explanation that the study results and published literature show the potential efficacy of mecobalamin in slowing the progression of ASL is understandable to a certain extent.

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

The applicant submitted the results from absorption, distribution, metabolism, and excretion studies in rats and dogs as non-clinical pharmacokinetic studies of mecobalamin. Concentrations of unchanged mecobalamin and its metabolites in biological samples were determined using liquid chromatography with tandem mass spectrometry (LC-MS/MS) (Lower limit of quantification [LLOQ], 10 ng/mL for unchanged mecobalamin and cobamamide, 30 ng/mL for hydroxocobalamin). In studies using ^{57}Co-labeled mecobalamin, radioactivity levels in biological samples were determined by a gamma counter (LLOQ, 3 times the difference between the maximum and minimum responses of blank samples).

4.1 Absorption

4.1.1 Single-dose studies

Table 4 shows the plasma pharmacokinetic parameters of unchanged mecobalamin or its metabolite following a single intravenous or intramuscular administration of mecobalamin in male rats or male dogs (CTD 4.2.2.2.1 and 4.2.2.2.2). A metabolite of mecobalamin, i.e., cobamamide was below the LLOQ at all time points. The absolute bioavailability of a 1 mg/kg intramuscular dose of mecobalamin in dogs was 99%.

Table 4. Plasma pharmacokinetic parameters of unchanged mecobalamin and its metabolite following a single intravenous or intramuscular administration of mecobalamin in rats or dogs

Animal species	Route of administration	Analyte	Dose (mg/kg)	Sex (Number of animals/group)	C_{max} (μg/mL)	t_{max} [a] (h)	AUC_{0-t} (μg·h/mL)	AUC_{inf} (μg·h/mL)	$t_{1/2}$ (h)	CTD
Rat	IV	Unchanged mecobalamin	1	4M	4.23 ± 0.22 [b]	—	3.62 ± 0.25	3.66 ± 0.25	0.78 ± 0.09	4.2.2.2.1
	IM		0.3	3M	0.42 ± 0.02	0.25 (0.25, 1.0)	0.74 ± 0.10	0.79 ± 0.07	0.66 ± 0.03	
			1	4M	1.68 ± 0.05	0.25 (0.25, 0.5)	2.82 ± 0.11	2.84 ± 0.11	0.66 ± 0.03	
			3	4M	5.36 ± 0.38	0.5 (0.5, 0.5)	7.93 ± 0.81	7.96 ± 0.82	0.71 ± 0.02	
	IV	Hydroxocobalamin	1	4M	0.07 ± 0.01	0.17 (0.08, 1.0)	0.06 ± 0.01	—	—	
	IM		1	4M	0.05 ± 0.004	2.0 (1.0, 2.0)	0.04 ± 0.01	—	—	
			3	4M	0.12 ± 0.02	1.5 (1.0, 2.0)	0.18 ± 0.02	—	—	
Dog	IV	Unchanged mecobalamin	1	3M	5.28 ± 0.23 [b]	—	5.50 ± 0.07	5.55 ± 0.08	1.30 ± 0.03	4.2.2.2.2
	IM		0.3	3M	0.73 ± 0.06	0.25 (0.25, 1.0)	1.77 ± 0.06	1.82 ± 0.06	1.54 ± 0.04	
			1	3M	2.42 ± 0.05	0.25 (0.25, 0.5)	5.38 ± 0.24	5.50 ± 0.27	1.48 ± 0.07	
			3	3M	8.19 ± 0.86	0.5 (0.5, 0.5)	18.92 ± 1.00	19.32 ± 1.05	1.49 ± 0.05	
	IV	Hydroxocobalamin	1	3M	0.13 ± 0.02	0.08 (0.08, 0.08)	0.16 ± 0.03	—	—	
	IM		1	3M	0.08 ± 0.02	1.0 (1.0, 2.0)	0.09 ± 0.02	—	—	
			3	3M	0.26 ± 0.03	1.0 (0.5, 1.0)	0.73 ± 0.10	—	—	

Mean ± SE; —, Not applicable or not calculated
a) Median (Min., Max.)
b) Plasma concentration at 5 minutes post-dose

4.1.2 Repeated-dose studies

The toxicokinetics of mecobalamin were evaluated in a repeated intramuscular dose toxicity study in rats. Table 5 shows the plasma pharmacokinetic parameters of unchanged mecobalamin following thrice weekly intramuscular administration of mecobalamin for 26 weeks (CTD 4.2.3.2.2).

Table 5. Plasma pharmacokinetic parameters of unchanged mecobalamin following repeated intramuscular administration of mecobalamin in rats

Sampling time point	Dose (mg/kg)	Sex (Number of animals/group)	C_{max} (μg/mL)	t_{max} (h)[a)]	$AUC_{0\text{-}24h}$ (μg·h/mL)	CTD
Day 1	5	M (n = 4	7.51 ± 1.05	0.50 (0.25, 0.5)	12.31 ± 3.40	4.2.3.2.2
		F (n = 4)	8.68 ± 0.87	0.50 (0.5, 0.5)	11.89 ± 1.87	
	10	M (n = 4)	12.71 ± 1.42	0.75 (0.25, 1.0)	23.76 ± 1.35	
		F (n = 4)	17.79 ± 1.26	0.50 (0.5, 0.5)	24.86 ± 4.95	
	20	M (n = 4)	25.48 ± 4.99	1.00 (0.5, 1.0)	53.91 ± 3.81	
		F (n = 4)	26.66 ± 3.33	0.50 (0.5, 0.5)	45.89 ± 6.00	
Day 26	5	M (n = 4)	6.92 ± 1.02	0.50 (0.5, 0.5)	11.37 ± 1.23	
		F (n = 4)	7.33 ± 1.11	0.38 (0.25, 0.5)	7.81 ± 3.37	
	10	M (n = 4)	12.75 ± 3.99	0.75 (0.5, 1.0)	26.02 ± 3.89	
		F (n = 4)	8.44 ± 1.66	0.38 (0.25, 0.5)	13.56 ± 2.72	
	20	M (n = 4)	22.70 ± 2.50	0.50 (0.5, 1.0)	50.68 ± 4.38	
		F (n = 4)	22.76 ± 2.56	0.38 (0.25, 1.0)	46.85 ± 4.49	
Day 180	5	M (n = 4)	17.17 ± 7.30	1.00 (0.5, 1.0)	164.62 ± 107.14	
		F (n = 3)	7.02 ± 1.17	0.50 (0.25, 0.5)	14.83 ± 2.19	
	10	M (n = 4)	14.60 ± 3.72	1.00 (0.5, 1.0)	85.95 ± 33.89	
		F (n = 4)	41.31 ± 24.72	1.00 (0.5, 1.0)	470.32 ± 412.34	
	20	M (n = 4)	31.97 ± 13.07	0.75 (0.5, 1.0)	245.22 ± 185.14	
		F (n = 4)	33.01 ± 6.03	0.50 (0.5, 0.5)	169.72 ± 91.56	

Mean ± SD
a) Median (Min., Max.)

4.2 Distribution

4.2.1 Tissue distribution

Following a single intramuscular administration of ^{57}Co-labeled mecobalamin 1 mg/kg in male albino rats (n = 3), tissue radioactivity concentrations at 0.5 to 168 hours post-dose were determined. Tissue radioactivity concentration peaked at 0.5 hours post-dose in all tissues evaluated,[4)] and the kidney, bladder, and abdominal aorta had radioactivity levels higher than plasma at 0.5 hours post-dose. At 168 hours post-dose, radioactivity was below the LLOQ in blood, plasma, and vein, but was quantifiable in other tissues. There were no major differences between radioactivity levels at 24 hours post-dose and at 168 hours post-dose, suggesting slow clearance of mecobalamin or its metabolites from tissues (CTD 4.2.2.3.1).

Following a single intramuscular administration of ^{57}Co-labeled mecobalamin 1 mg/kg in male dogs (n = 3), tissue radioactivity concentrations at 0.5 to 168 hours post-dose were determined. In all tissues evaluated[5)] except for bile, tissue radioactivity concentration peaked at 0.5 hours post-dose, and bladder urine, renal medulla, injection site skeletal muscle, kidney, renal cortex, vein, and abdominal aorta had radioactivity levels higher than plasma at 0.5 hours post-dose. At 168 hours post-dose, radioactivity was still quantifiable in all tissues, except for blood, plasma, blood cells, cerebrum, cerebellum, anterior chamber humor, lens, and vitreous body (CTD 4.2.2.3.2).

4) blood, plasma, blood cells, brain, spinal cord, pituitary gland, eyes, Harderian gland, submandibular gland, thyroid gland, trachea, thymus, heart, lungs, liver, spleen, pancreas, mesenteric lymph nodes, adrenal gland, kidneys, testis, prostate gland, bladder, abdominal aorta, vein, sciatic nerve, skeletal muscle (non-injection site), skeletal muscle (injection site), skin, fat, stomach, duodenum, small intestine, large intestine, cecum

5) blood, plasma, blood cells, cerebrum, cerebellum, spinal cord, pituitary gland, submandibular gland, submandibular lymph nodes, trachea, thymus, sciatic nerve, prostate gland, thyroid gland, heart, lungs, abdominal aorta, vein, liver, gallbladder, bile, spleen, pancreas, adrenal gland, kidneys, renal medulla, renal cortex, testis, bladder, bladder urine, stomach, duodenum, jejunum, ileum, cecum, large intestine, fat, skin, bone marrow, skeletal muscle (non-injection site), skeletal muscle (injection site), anterior chamber humor, cornea, lens, iris, ciliary body, vitreous body, choroid, retina, sclera, optic nerve

4.2.2 Protein binding

Rat or dog plasma was spiked with ^{57}Co-labeled mecobalamin (30, 300, and 3000 ng/mL), and the plasma protein binding was determined using an ultrafiltration method. At 30, 300, and 3000 ng/mL, the percentages of mecobalamin bound to plasma proteins were 29.9%, 24.0%, and 21.0%, respectively, in the rat and 36.9%, 27.6%, and 26.7%, respectively, in the dog (CTD 5.3.2.1.1).

4.2.3 Placental transfer

Following a single intramuscular administration of ^{57}Co-labeled mecobalamin (1 mg/kg) in rats on gestation day 12 (n = 3), mecobalamin crossed the placenta. The mean radioactivity concentrations in maternal plasma, placenta, uterus, and ovary at 0.5 hours post-dose were 1.4545 μg eq./mL, 0.4325 μg eq./g, 0.7596 μg eq./g, and 0.4145 μg eq./g, respectively, and the fetal tissue concentration was 0.0181 μg eq./g. At 168 hours post-dose, although radioactivity in maternal plasma was below the LLOQ, radioactivity was quantifiable in maternal placenta, uterus, and ovary and fetal tissue. The clearance of radioactivity occurred slowly (CTD 4.2.2.3.1).

4.3 Metabolism

Following a single intramuscular administration of ^{57}Co-labeled mecobalamin 1 mg/kg in male rats (n = 3), only unchanged mecobalamin was detected in plasma and skeletal muscle, and unchanged mecobalamin and hydroxocobalamin were found in the liver, at 0.5 hours post-dose. Unchanged mecobalamin, hydroxocobalamin, and cobamamide were detected in the kidney up to 168 hours post-dose. Unchanged mecobalamin (89% of the administered radioactivity) and hydroxocobalamin (<1% of the administered radioactivity) were found in urine up to 8 hours post-dose (CTD 4.2.2.4.1).

Following a single intramuscular administration of ^{57}Co-mecobalamin 1 mg/kg in male dogs (n = 3), only unchanged mecobalamin was detected in plasma up to 2 hours post-dose and in the skeletal muscle and kidney at 0.5 hours post-dose, and unchanged mecobalamin**,** hydroxocobalamin, and cobamamide were found in the renal medulla at 0.5 hours post-dose. Unchanged mecobalamin (94.9% of the administered radioactivity) was detected in urine up to 8 hours post-dose, and approximately 99% of the administered radioactivity was excreted unchanged in urine up to 24 hours post-dose (CTD 4.2.2.4.1).

4.4 Excretion

4.4.1 Urinary, fecal, and biliary excretion

Following a single intramuscular administration of ^{57}Co-labeled mecobalamin 1 mg/kg in male rats (n = 3), 91.6% and 4.2% of the administered radioactivity were excreted in urine and feces, respectively, over 168 hours. Following a single intramuscular administration of ^{57}Co-labeled mecobalamin 1 mg/kg in bile duct-cannulated male rats (n = 3), 0.1% and 91.4% of the administered radioactivity were excreted in bile and urine, respectively, over 48 hours, and radioactivity was not recovered in feces (CTD 4.2.2.3.1).

4.4.2 Excretion into milk

Following a single intramuscular administration of ^{57}Co-labeled mecobalamin 1 mg/kg in lactating rats (n = 3), the maximum concentration of radioactivity in milk was observed at 2 hours post-dose, and the radioactivity concentrations in milk and maternal blood at 2 hours post-dose were 0.44 μg eq./g and 0.34 μg eq./mL, respectively. At 72 hours post-dose, radioactivity in maternal blood was below the LLOQ, but the radioactivity concentration in milk was 0.017 μg eq./g (CTD 4.2.2.3.1).

4.R Outline of the review conducted by PMDA

PMDA concluded that there is no particular problem with the submitted non-clinical pharmacokinetic data.

5. Toxicology and Outline of the Review Conducted by PMDA

The applicant submitted the results from repeated intramuscular dose toxicity studies in rats or dogs and rodent micronucleus assay and the results of safety assessment of impurities in the drug product.

5.1 Repeated-dose toxicity

Since the daily dose of the proposed product far exceeds the dose of the currently approved intramuscular or intravenous formulation containing mecobalamin, repeated intramuscular dose toxicity studies in rats (2 weeks and 6 months) and a repeated intramuscular dose toxicity study in dogs (2 weeks) were conducted (Table 6). The noteworthy finding was chromaturia (red) caused by the pigment of the test substance.

Mecobalamin exposure (AUC [the mean of males and females], 207.47 μg·h/mL) at the no-observed-adverse-effect-level (NOAEL) in a 6-month repeated intramuscular dose toxicity study in rats (20 mg/kg) was approximately 23-fold the estimated human exposure (AUC = 8.84 μg·h/mL) at the clinical dose (50 mg). Mecobalamin exposure (AUC [the mean of males and females], 30.65 μg·h/mL) at the NOAEL in a 2-week repeated intramuscular dose toxicity study in dogs was approximately 3.5-fold the estimated human exposure (AUC = 8.84 μg·h/mL) at the clinical dose (50 mg).

Table 6. Overview of repeated-dose toxicity studies

Test system	Route of administration	Duration of dosing	Doses (mg/kg/day)	Noteworthy findings	NOAEL (mg/kg/day)	CTD
Male and female rats (SD)	IM	2 weeks (once daily)	0,[a] 5, 10, 20	≥5: chromaturia (red)	20	4.2.3.2.1
Male and female rats (SD)	IM	6 months (thrice weekly, every other day)	0,[a] 5, 10, 20	≥5: chromaturia (red)	20	4.2.3.2.2
Male and female dogs (beagle)	IM	2 weeks (once daily)	0,[a] 2.5, 6.25	≥2.5: chromaturia (red)	6.25	4.2.3.2.3
Male and female dogs (beagle)	IV	12 months (once daily)	0,[b] 0.5, 5, 50	≥5: chromaturia (red), reddish discoloration of the renal cortex/epididymis, deposition of eosinophilic granules within the proximal tubular epithelium of the kidneys 50: flushed skin, transient papules, reddish discoloration of the prostate gland	5[c]	Reference data 4.2.3.2.5

a) Vehicle: 6.25% lactose, 0.1725% sodium phosphate, 0.9% sodium chloride, pH7.0
b) Vehicle: 5% mannitol
c) The applicant concluded that the findings at 5 mg/kg were physiological adaptive changes and were not adverse.

5.2 Genotoxicity

As part of the marketing application for the currently approved intramuscular or intravenous formulation containing mecobalamin, the applicant submitted the data from Ames and *in vitro* chromosomal aberration assays of mecobalamin, both of which produced negative results. For the present application, rat micronucleus assay was performed, and mecobalamin was not genotoxic (Table 7).

Table 7. Overview of genotoxicity study

Type of study		Test system	Doses (mg/kg/day)	Test result	CTD
In vivo	Rodent micronucleus assay	Male rat (SD) bone marrow	0,[s] 50, 125, 250 (IV, single dose)	Negative	4.2.3.3.2.1

a) Vehicle: 6.25% lactose, 0.1725% sodium phosphate, 0.9% sodium chloride, pH7.0

5.3 Carcinogenicity

No results from carcinogenicity studies of mecobalamin were submitted. The recommended clinical dose of the proposed product (i.e., Rozebalamin) is approximately 100 times higher than those of the currently approved formulations, and the proposed product is intended to be administered to humans for long periods. There are various reports on the association between vitamin B_{12} and cancer risk (*Cancer Manag Res*. 2018; 10: 5395-410, *Cancer Epidemiol Biomarkers Prev*. 2019; 28: 814-21, *Nutrients*. 2022; 14: 4476). Given these points, since it is difficult to draw a definitive conclusion on whether vitamin B_{12}, mecobalamin, has carcinogenic potential, the applicant plans to conduct carcinogenicity studies. The carcinogenic risk of mecobalamin will be discussed in Section 5.R.1.

5.4 Local tolerance

The local tolerance of mecobalamin was evaluated in repeated intramuscular dose toxicity studies in rats (2 weeks and 6 months) and a repeated intramuscular dose toxicity study in dogs (2 weeks). No local irritation at the injection site was observed.

5.5 Safety assessment of impurities

The applicant's explanation about the systemic and local toxicities of hydroxocobalamin, i.e., an impurity in the drug product with an acceptance criterion of greater than the qualification threshold specified in the ICH Q3B guideline:

Given that there were no safety concerns in dogs following 14-week intramuscular administration of hydroxocobalamin 1 mg (JP, Drug Information, JPDI2006. *Jiho*; 2006: 1347-9) and based on the clinical experience with the pharmaceutical products containing the active substance hydroxocobalamin in foreign countries and Japan, there is no problem with the safety of this impurity at the specification limit.

5.R Outline of the review conducted by PMDA

5.R.1 Carcinogenicity

The applicant's explanation about the carcinogenic potential of mecobalamin:

Since ALS is a life-threatening, serious disease, the results from carcinogenicity studies will be submitted after marketing of the proposed product so that the proposed product will be made available in clinical practice as soon as possible. The currently available study results shown below have not suggested the carcinogenic risk of mecobalamin.

- In a 6-month intramuscular dose toxicity study in rats (CTD 4.2.3.2.2) and a 12-month intravenous dose toxicity study in dogs, which was submitted as part of the marketing application for the currently approved intramuscular or intravenous formulation containing mecobalamin (CTD 4.2.3.2.5), there were no changes that were considered to be chronic inflammation or preneoplastic lesions, or findings indicative of hormonal changes or immunosuppression.
- Mecobalamin was negative for genotoxicity [see Section 5.2].
- The malignancy rates were determined in clinical studies with >1 year of exposure to the proposed product. The malignancy rates were 0.42 per 100 patient-years in the mecobalamin 50 mg group, 0.83 per 100 patient-years in the mecobalamin 25 mg group, and 1.28 per 100 patient-years in the placebo group in Japanese Study 761 and 0.49 per 100 patient-years in patients treated with mecobalamin in Japanese Study 763 (the entire period [[redacted] 20[redacted] data cutoff]). A causal relationship to mecobalamin was ruled out for all malignancy cases.

The following study reports will be submitted in future: a carcinogenicity study in rats (planned to be completed in the 1st quarter of 2028) based on the results of the ongoing 30-week subcutaneous dose-finding study in rats; and a carcinogenicity study in rasH2 mice (planned to be completed in 2030) or a carcinogenicity study in mice (planned to be completed in 2033) based on the results of the planned subcutaneous dose-finding study in mice.

PMDA's view:

Mecobalamin is negative for genotoxicity, and there were no preneoplastic lesions in repeated-dose toxicity studies. Given these and other findings, no information indicative of the carcinogenic risk of mecobalamin has

been obtained at present. Taking also into account that ALS is a relatively rapidly progressive, serious disease, and that treatment options for ALS patients are very limited at present, the clinical use of mecobalamin is acceptable even though the non-clinical assessment of carcinogenic potential of mecobalamin has not been completed. However, carcinogenicity studies in rats and mice should be conducted as soon as possible, and if any finding indicative of carcinogenicity of mecobalamin is observed, the relevant information should be provided promptly to healthcare professionals in clinical practice, and then the need for additional safety measures, etc., should be determined.

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

6.1 Summary of biopharmaceutic studies and associated analytical methods

No data from biopharmaceutic studies have been submitted.

Concentrations of unchanged mecobalamin in biological samples were determined by HPLC-UV/VIS or LC-MS/MS (LLOQ, 25 ng/mL).

A lyophilized formulation was used in clinical studies of mecobalamin. During development, sodium dihydrogen phosphate monohydrate, which was used as a pH adjuster in the drug product, was changed to sodium dihydrogen phosphate dihydrate; however, the amount of sodium dihydrogen phosphate remained unchanged. The formulation of the drug product used in a Japanese phase III study (Japanese Study 763) contained sodium dihydrogen phosphate dihydrate, and the to-be-marketed drug product in Japan has the same formulation as that of the drug product used in the Japanese phase III study.

6.2 Clinical pharmacology

6.2.1 Studies using human biomaterials

(1) Plasma protein binding

Human plasma was spiked with ^{57}Co-labeled mecobalamin (3-3000 ng/mL), and the plasma protein binding was determined using an ultrafiltration method. At 3, 30, 300, and 3000 ng/mL, the percentages of mecobalamin bound to plasma proteins were 76.1%, 35.8%, 27.8%, and 25.0%, respectively. Human serum albumin (4%) or α1-acid glycoprotein (0.05%) was spiked with ^{57}Co-labeled mecobalamin (3-3000 ng/mL), and the plasma protein binding was determined using an ultrafiltration method. At 3, 30, 300, and 3000 ng/mL, the percentages of mecobalamin bound to human serum albumin were 27.0%, 7.4%, 6.2%, and 4.5%, respectively, and the percentages of mecobalamin bound to α1-acid glycoprotein were 25.2%, 4.1%, 6.2%, and 3.7%, respectively. After human plasma, human serum albumin, and α1-acid glycoprotein were spiked with ^{57}Co-labeled mecobalamin, the binding protein of mecobalamin was predicted by gel filtration chromatography, which suggested that transcobalamin contributes to mecobalamin binding (CTD 5.3.2.1.1).

(2) Enzyme inhibition or induction

Using the specific substrates for cytochrome P450 isoforms,[6] the potential of mecobalamin (3-100 μmol/L) to inhibit these isoforms in human liver microsomes was evaluated. Mecobalamin caused no evident inhibition of the metabolism of any of the substrates for the CYP isoforms at the concentrations tested (CTD 5.3.2.2.1).

Human hepatocytes were treated with mecobalamin (10-100 μmol/L), and the potential of mecobalamin to induce CYP1A2, CYP2B6, and CYP3A4 was evaluated based on mRNA expression. Mecobalamin caused no evident induction of any of the CYP isoforms at the concentrations tested (CTD 5.3.2.2.2).

(3) Drug transporter inhibition potential

Using membrane vesicles expressing human P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP), the potential of mecobalamin (1-100 μmol/L) to inhibit the transport of the typical substrates of these transporters[7] was evaluated. Mecobalamin caused no evident inhibition of the transport of the substrates of P-gp and BCRP. Using human embryonic kidney 293 (HEK293) cell line expressing organic anion transporting polypeptide 1B1 (OATP1B1), OATP1B3, organic anion transporter 1 (OAT1), OAT3, organic cation transporter 1 (OCT1), OCT2, multidrug and toxin extrusion 1 (MATE1), or MATE2-K, the potential of mecobalamin (1-100 μmol/L) to inhibit the transport of the typical substrates of these transporters[8] was evaluated. Mecobalamin caused no evident inhibition of the transport of any of the substrates of these transporters (CTD 5.3.2.3.1).

6.2.2 Healthy adult subject studies

6.2.2.1 Phase I study (Reference data CTD 5.3.3.1.1, Study E0302-E044-001)

Table 8 shows the pharmacokinetic parameters of mecobalamin following single intramuscular doses of mecobalamin 25 to 75 mg in Japanese and non-Japanese healthy adult subjects (36 subjects included in pharmacokinetic assessment).

Table 8. Plasma pharmacokinetic parameters of unchanged mecobalamin following administration of mecobalamin in healthy adult subjects

	Dose (mg)	Number of subjects evaluated	C_{max} (μg/mL)	t_{max}[a] (h)	AUC_{0-t} (μg·h/mL)	AUC_{0-inf} (μg·h/mL)	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)
Japanese	25	6	0.83 ± 0.13	2.0 (0.8, 2.0)	4.22 ± 0.52	4.27 ± 0.53	3.1 ± 1.0	5.93 ± 0.73	25.60 ± 6.25
	50	6	1.66 ± 0.31	1.0 (0.8, 2.0)	8.45 ± 1.08	8.45 ± 1.07	2.8 ± 0.4	5.99 ± 0.77	24.77 ± 5.43
	75	6	2.31 ± 0.26	2.0 (1.0, 2.0)	12.56 ± 1.09	12.58 ± 1.11	3.0 ± 0.4	6.00 ± 0.50	26.21 ± 4.02
Non-Japanese	25	6	0.80 ± 0.12	1.5 (1.0, 3.0)	3.60 ± 0.56	3.67 ± 0.57	2.5 ± 0.2	6.96 ± 1.12	24.83 ± 4.60
	50	6	1.38 ± 0.32	2.0 (1.0, 2.0)	7.92 ± 1.61	7.93 ± 1.54	3.4 ± 0.2	6.50 ± 1.19	31.60 ± 5.87
	75	6	2.02 ± 0.47	2.0 (1.0, 2.0)	11.50 ± 2.22	11.50 ± 2.14	3.6 ± 0.8	6.70 ± 1.15	34.18 ± 8.78

Mean ± SD

a) Median (Min., Max.)

6) 7-ethoxyresorufin 0.5 μmol/L for CYP1A2; coumarin 2 μmol/L for CYP2A6; bupropion 150 μmol/L for CYP2B6; paclitaxel 5 μmol/L for CYP2C8; tolbutamide 400 μmol/L for CYP2C9; *S*-mephenytoin 100 μmol/L for CYP2C19; bufuralol 20 μmol/L for CYP2D6; chlorzoxazone 100 μmol/L for CYP2E1; nifedipine 15 μmol/L, midazolam 10 μmol/L, or testosterone 150 μmol/L for CYP3A

7) ^{3}H-N-methyl quinidine 5 μmol/L for P-gp; ^{3}H-methotrexate 100 μmol/L for BCRP

8) ^{3}H-estradiol 17β-D-glucuronide 0.05 μmol/L for OATP1B1 and OATP1B3; ^{3}H-*p*-aminohippuric acid 1 μmol/L for OAT1; ^{3}H-estrone 3-sulfate 0.05 μmol/L for OAT3; ^{14}C-metformin 10 μmol/L for OCT1, OCT2, MATE1, and MATE2-K

6.2.2.2 Phase I study (Reference data CTD 5.3.3.1.2, Study E0302-E044-002)

Table 9 shows the pharmacokinetic parameters of mecobalamin following once daily intramuscular administration of mecobalamin 25 or 50 mg for 7 days in Japanese and non-Japanese healthy adult subjects (24 subjects included in pharmacokinetic assessment). There were no increases in exposure after once daily dosing.

Table 9. Plasma pharmacokinetic parameters of unchanged mecobalamin following administration of mecobalamin in healthy adult subjects

	Dose (mg)	Sampling time point	Number of subjects evaluated	C_{max} (μg/mL)	t_{max} [a)] (h)	$AUC_{0\text{-}24h}$ (μg·h/mL)	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)
Japanese	25	Day 1	6	0.85 ± 0.26	1.0 (1.0, 2.0)	4.43 ± 0.52	2.7 ± 0.4	5.69 ± 0.64	22.03 ± 4.70
		Day 7	6	0.93 ± 0.20	1.0 (0.8, 2.0)	4.32 ± 0.52	2.6 ± 0.6	5.83 ± 0.66	22.42 ± 6.87
	50	Day 1	6	1.49 ± 0.32	1.0 (0.8, 3.0)	8.85 ± 1.04	2.9 ± 0.2	5.69 ± 0.67	24.26 ± 4.10
		Day 7	6	1.58 ± 0.26	1.0 (0.8, 2.0)	8.84 ± 0.65	2.8 ± 0.3	5.66 ± 0.42	23.17 ± 3.40
Non-Japanese	25	Day 1	6	0.70 ± 0.16	1.5 (1.0, 2.0)	3.85 ± 0.62	2.7 ± 0.3	6.62 ± 1.08	25.68 ± 5.10
		Day 7	6	0.72 ± 0.24	1.5 (1.0, 2.0)	3.66 ± 0.63	2.9 ± 0.6	6.97 ± 1.20	29.10 ± 7.72
	50	Day 1	6	1.40 ± 0.27	1.0 (1.0, 2.1)	7.76 ± 1.21	3.0 ± 0.4	6.54 ± 1.00	27.80 ± 5.42
		Day 7	6	1.39 ± 0.26	2.0 (1.0, 2.0)	8.16 ± 1.21	2.9 ± 0.4	6.22 ± 0.99	25.70 ± 4.40

Mean ± SD
a) Median (Min., Max.)

6.2.3 Patient studies

6.2.3.1 Japanese phase III study (CTD 5.3.5.1.2 and 5.3.5.1.3, Study E0302-TOK-763)

The pharmacokinetics of mecobalamin were evaluated in 8 ALS patients on extended treatment with twice weekly intramuscular mecobalamin 50 mg (1 patient with normal renal function,[9)] 4 patients with mild renal impairment,[10)] 3 patients with moderate renal impairment[11)]) during the extension phase of a Japanese phase III study (Japanese Study 763). Table 10 shows the pharmacokinetic parameters of mecobalamin.

Table 10. Pharmacokinetic parameters following twice weekly intramuscular administration of mecobalamin 50 mg in subjects with normal renal function or renal impairment

Renal function	Number of subjects evaluated	C_{max} (μg/mL)	t_{max} [a)] (h)	$AUC_{0\text{-}8h}$ (μg·h/mL)	$t_{1/2}$ (h)	CL/F (L/h)
Normal	1	1.44	2.0	6.78	2.71	6.21
Mild	4	1.83 ± 0.62	1.5 (0.5, 2.0)	8.29 ± 3.17	2.91 ± 0.57	5.45 ± 1.68
Moderate	3	2.16 ± 0.88	2.0 (1.0, 4.0)	10.60 ± 1.93	3.25[b)]	4.42[b)]

Mean ± SD
Individual values are listed for n = 1.
a) Median (Min., Max.), b) n = 1

6.R Outline of the review conducted by PMDA

6.R.1 Use of mecobalamin in patients with renal impairment

The applicant's explanation about the use of mecobalamin in patients with renal impairment:

Although the impact of decreased renal function on the pharmacokinetics of mecobalamin was evaluated during the extension phase of a Japanese phase III study (Japanese Study 763), the PK data from a phase I study in Japanese healthy adult subjects (Foreign Study 002) were also used for comparison because only 1

9) Serum cystatin C-based glomerular filtration rate of ≥90 mL/min/1.73 m^2
10) Serum cystatin C-based glomerular filtration rate of 60-89 mL/min/1.73 m^2
11) Serum cystatin C-based glomerular filtration rate of 30-59 mL/min/1.73 m^2

subject had normal renal function in this analysis. The results are shown in Table 11, and the C_{max} and AUC of mecobalamin tended to increase with decreasing renal function.

Table 11. Pharmacokinetic parameters following administration of mecobalamin in subjects with normal renal function or renal impairment

Study ID	Renal function	Number of subjects evaluated	C_{max} (μg/mL)	$AUC_{0\text{-}8h}$ (μg·h/mL)
Foreign Study 002	Normal	6	1.58 ± 0.26 1.52 (1.31, 1.97)	7.59 ± 0.68 7.45 (6.75, 8.70)
Japanese Study 763	Normal	1	1.44	6.78
	Mild renal impairment	4	1.83 ± 0.62 1.74 (1.29, 2.56)	8.29 ± 3.17 7.77 (5.18, 12.50)
	Moderate renal impairment	3	2.16 ± 0.88 1.74 (1.57, 3.17)	10.60 ± 1.93 10.4 (8.80, 12.60)

Upper row, Mean ± SD; Lower row, Median (Min., Max.)
Individual values are listed for n = 1.

Table 12 shows the incidences of adverse events in patients with normal renal function, patients with mild renal impairment, and patients with moderate renal impairment during the treatment and extension phases of Japanese Study 763. There were no major differences in the incidence of adverse events, including the nature of the reported events, according to the degree of renal impairment.

Table 12. Incidence of adverse events by degree of renal impairment (Japanese Study 763)

	Patients with normal renal function (N = 36)	Patients with mild renal impairment (N = 21)	Patients with moderate renal impairment (N = 8)
Treatment phase			
All adverse events	23 (63.9)	11 (52.4)	6 (75.0)
Serious adverse events	1 (2.8)	0	0
Extension phase			
All adverse events	33 (91.7)	19 (90.5)	7 (87.5)
Serious adverse events	15 (41.7)	9 (42.9)	3 (37.5)

n (%)

There are no data concerning the impact of severe renal impairment on the pharmacokinetics of mecobalamin, and the extent of increase in mecobalamin exposure is unknown. However, 1 patient with severe renal impairment and 2 patients with severe renal impairment in Japanese Studies 762 and 763, respectively, were treated with mecobalamin for a long period of time. Adverse events reported by these subjects are shown in Table 13. A causal relationship to study drug was ruled out for all those events, and there were no major safety issues related to the use of mecobalamin.

Table 13. Adverse events occurring following administration of mecobalamin in patients with severe renal impairment

Study ID	Age, Sex	Co-morbidity	Duration of mecobalamin administration	Adverse events
Japanese Study 762	A male patient in his 60s	Nephrotic syndrome	≥1500 days	pain in extremity, hypoaesthesia, constipation, hypertension, periodontitis*, nephrotic syndrome*, diabetes mellitus, cheilitis, fall, contusion, spinal compression fracture, dental caries, tinea versicolour, epistaxis, tinea pedis, eczema, nasopharyngitis*, skin fissures, hepatic steatosis, gastritis, post procedural complication, blepharitis, myalgia, pneumonia aspiration*, upper respiratory tract inflammation, urticaria, application site abscess*, application site inflammation, decubitus ulcer, dermatitis allergic
Japanese Study 763	A male patient in his 60s	Chronic kidney disease	181 weeks	arthralgia, diabetes mellitus, liver disorder, fall, skin abrasion, contusion
	A male patient in his 60s	Chronic kidney disease	105 weeks	cystitis, constipation, femoral neck fracture*

*: Serious adverse events

Based on the above, though there is limited clinical experience with mecobalamin in patients with severe renal impairment, no dosage adjustment of mecobalamin is required in patients with renal impairment including those with severe renal impairment, and a precautionary statement regarding the use of mecobalamin in patients with renal impairment should be unnecessary.

PMDA's view:

Renal excretion is the primary pathway for clearance of mecobalamin [see Section 4.3], and the package insert should advise that mecobalamin exposure tended to increase according to the degree of renal impairment in Japanese Study 763. On the other hand, when patients with renal impairment including those with severe renal impairment were treated with mecobalamin, there were no particular safety issues related to the use of mecobalamin although the number of patients was small. Given this and other findings, no dosage adjustment of mecobalamin is required in patients with renal impairment.

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

The applicant submitted the results from clinical studies presented in Table 14 as the main efficacy and safety data.

Table 14. Listing of main efficacy and safety clinical studies

Data category	Geographical location	Study ID CTD	Phase	Study population	Number of subjects enrolled	Dosing regimen	Main endpoints
Evaluation	Japan	Study E0302-J081-761 5.3.5.1.1	II/III	ALS patients	373	Placebo or mecobalamin 25 or 50 mg administered intramuscularly twice weekly	Efficacy Safety
	Japan	Study E0302-J081-762 5.3.5.2.1 to 5.3.5.2.4	III	ALS patients	149	Mecobalamin 50 mg administered intramuscularly twice weekly	Safety Efficacy
	Japan	Study E0302-TOK-763 5.3.5.1.2 and 5.3.5.1.3	III	ALS patients	130	Treatment phase: Placebo or mecobalamin 50 mg administered intramuscularly twice weekly Extension phase: Mecobalamin 50 mg administered intramuscularly twice weekly	Efficacy Safety

7.1 Phase I studies

7.1.1 Foreign phase I study (Reference data CTD 5.3.3.1.1, Study E0302-E044-001 [[redacted] to [redacted]])

A placebo-controlled, randomized, double-blind, ascending single-dose study was conducted to evaluate the safety and pharmacokinetics of a single intramuscular dose of mecobalamin in Japanese and non-Japanese healthy adult subjects (target sample size, 48 subjects [16 per cohort]) [for pharmacokinetics, see Section 6.2.2.1].

A single intramuscular dose of placebo or mecobalamin 25, 50, or 75 mg was to be administered in each cohort. Subjects in each cohort (n = 16) were randomized to receive placebo (4 subjects) or mecobalamin (12 subjects).

All of 48 subjects who were randomized and received study drug (12 in the placebo group, 36 in the mecobalamin group) were included in the safety analysis set. There was 1 discontinuation, and the reason for discontinuation was lost to follow-up.

Regarding safety, the incidences of adverse events were 50.0% (6 of 12 subjects) in the placebo group, 16.7% (2 of 12 subjects) in the mecobalamin 25 mg group, 25% (3 of 12 subjects) in the mecobalamin 50 mg group, and 16.7% (2 of 12 subjects) in the mecobalamin 75 mg group. There were no serious adverse events including deaths or adverse events leading to treatment discontinuation.

The reported adverse events were nausea (0 subjects in the placebo group, 0 subjects in the mecobalamin 25 mg group, 0 subjects in the mecobalamin 50 mg group, 1 subject in the mecobalamin 75 mg group, the same order applies hereinafter), feeling hot (0 subjects, 1 subject, 0 subjects, 0 subjects), nasopharyngeal pain (2 subjects, 0 subjects, 1 subject, 1 subject), musculoskeletal stiffness (0 subjects, 1 subject, 0 subjects, 0 subjects), pain in extremity (0 subjects, 0 subjects, 0 subjects, 1 subject), dizziness (0 subjects, 1 subject, 0 subjects, 0 subjects), headache (2 subjects, 1 subject, 1 subject, 2 subjects), dry skin (0 subjects, 0 subjects, 1 subject, 0 subjects), eczema (1 subject, 0 subjects, 0 subjects, 0 subjects), abdominal distension (1 subject, 0 subjects, 0 subjects, 0 subjects), diarrhoea (1 subject, 0 subjects, 0 subjects, 0 subjects), influenza like illness (1 subject, 0 subjects, 0 subjects, 0 subjects), and injection site pain (0 subjects, 0 subjects, 1 subject, 0 subjects).

7.1.2 Foreign phase I study (Reference data CTD 5.3.3.1.2, Study E0302-E044-002 [[redacted] to [redacted]])

A placebo-controlled, randomized, double-blind, ascending multiple-dose study was conducted to evaluate the safety and pharmacokinetics of mecobalamin following multiple intramuscular administration of mecobalamin in Japanese and non-Japanese healthy adult subjects (target sample size, 36 subjects [18 per cohort]) [for pharmacokinetics, see Section 6.2.2.2].

Placebo or mecobalamin 25 or 50 mg was to be administered intramuscularly once daily for 7 days in each cohort. Subjects in each cohort (n = 18) were randomized to receive placebo (6 subjects) or mecobalamin (12 subjects).

All of 36 subjects who were randomized and received study drug (12 in the placebo group, 24 in the mecobalamin group) were included in the safety analysis set, and there were no discontinuations.

Regarding safety, the incidences of adverse events were 25.0% (3 of 12 subjects) in the placebo group, 50.0% (6 of 12 subjects) in the mecobalamin 25 mg group, and 50.0% (6 of 12 subjects) in the mecobalamin 50 mg group. There were no serious adverse events including deaths or adverse events leading to treatment discontinuation.

The reported adverse events were catheter site pain (0 subjects in the placebo group, 2 subjects in the mecobalamin 25 mg group, 2 subjects in the mecobalamin 50 mg group), dizziness (0 subjects, 1 subject, 1 subject), headache (1 subject, 2 subjects, 1 subject), syncope (1 subject, 0 subjects, 0 subjects), acne (0 subjects, 0 subjects, 1 subject), dermatitis acneiform (0 subjects, 0 subjects, 1 subject), diarrhoea (0 subjects, 0 subjects, 1 subject), constipation (1 subject, 1 subject, 0 subjects), vulvovaginal discomfort (0 subjects, 0 subjects, 1 subject), and venipuncture site contusion (1 subject, 0 subjects, 0 subjects).

7.2 Japanese phase II/III study (CTD 5.3.5.1.1, Study E0302-J081-761 [December 2006 to March 2014])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to evaluate the efficacy and safety of mecobalamin in Japanese patients with ALS aged ≥20 years (target sample size, 360 subjects [120 per group[12)]]).

The key inclusion criteria: “clinically definite ALS,” “clinically probable ALS,” or “clinically probable-laboratory-supported ALS” according to the revised El Escorial criteria (Airlie House criteria)[13)]; grade 1 or 2

12) Assuming a hazard ratio of the primary endpoint of events (full-time non-invasive ventilation, invasive ventilation, or death) of 0.5 to 0.6, an annual event rate of 0.50 to 0.55, and an effect size in the ALSFRS-R analysis of 0.3 to 0.4 (i.e., standardized treatment difference = treatment difference/standard deviation of the change), simulations were performed for a one-sided significance level of 1% with a power of ≥90% for at least 1 of 4 contrasts. The target total number of events was 200, and the initial target sample size was 300 subjects (100 per group). Since the annual event rate was lower than anticipated according to the blinded data monitoring during the clinical study, the target sample size was changed to 360 subjects (120 per group).

13) The revised El Escorial criteria (Airlie House criteria) (*Clinical neurology*. 2002; 42: 678-719) classify patients into the following 5 levels of diagnostic certainty.

1. Clinically Definite ALS: Clinical evidence of upper motor neuron and lower motor neuron signs in 3 regions
2. Clinically Probable ALS: Clinical evidence of upper motor neuron and lower motor neuron signs in at least 2 regions with some upper motor neuron signs necessarily rostral to the lower motor neuron signs
3. Clinically Probable-laboratory-supported ALS: Clinical signs of upper motor neuron and lower motor neuron dysfunction in only 1 region, or upper motor neuron signs in 1 region, and needle electromyographic signs of acute denervation in at least 2 muscles innervated by different routes or nerves in 2 limbs, with neuroimaging and clinical laboratory investigations to exclude other causes
4. Clinically Possible ALS: Clinical signs of upper motor neuron and lower motor neuron dysfunction in only 1 region or upper motor neuron signs alone in 2 or more regions or lower motor neuron signs rostral to upper motor neuron signs and the diagnosis of Clinically Probable-laboratory-supported ALS cannot be proven. Other diagnoses must be excluded to accept a diagnosis of clinically possible ALS.
5. Clinically Suspected ALS: A pure lower motor neuron syndrome, where the diagnosis of ALS could not be regarded as sufficiently certain to include the patient in a research study. This category has been deleted in the revised El Escorial criteria (Airlie House criteria).

of the ALS severity classification[14]; %FVC (forced vital capacity) >60%; and ≤3 years since ALS symptom onset at the start of the run-in period; and a 1- to 3-point decline in the ALS functional rating scale-revised (ALSFRS-R)[15] total score over the run-in period.

The study consisted of a run-in phase (12 weeks), a study drug delivery phase (up to 2 weeks), and a treatment phase (182 weeks). Placebo or mecobalamin 25 or 50 mg was to be administered intramuscularly twice weekly for 182 weeks.[16]

The randomization was stratified by onset type (bulbar or upper or lower limb onset), riluzole coadministration, the ALSFRS-R total score at the end of the run-in period (≤37 points, 38-42 points, ≥43 points), and the change in the ALSFRS-R total score over the run-in period (1 point, 2 points, or 3 points). Subjects were equally randomized to receive mecobalamin 25 mg, mecobalamin 50 mg, or placebo.

Among 373 randomized subjects (124 in the placebo group, 124 in the mecobalamin 25 mg group, 125 in the mecobalamin 50 mg group), 370 subjects (123 subjects, 124 subjects, 123 subjects) were included in the safety analysis set and in the full analysis set (FAS), and the FAS was used as the efficacy analysis set. The remaining 3 subjects who did not satisfy the diagnostic criteria (1 subject, 0 subjects, 2 subjects) were excluded from the analyses. There were 113 discontinuations (38 subjects, 36 subjects, 39 subjects), and the main reasons for discontinuations were the subject's refusal to continue participation in the clinical study (60 subjects [21 subjects, 16 subjects, 23 subjects]), decision by the investigator etc. (14 subjects [6 subjects, 3 subjects, 5 subjects]), etc.

The primary endpoints were the time to event[17] from the enrollment in the treatment phase (days) and the change in the ALSFRS-R total score from the end of the run-in period to the last time point. For multiplicity adjustment, the permutation-adjusted *P*-values[18] for the 4 contrasts were calculated and compared with the level of significance (one-sided, 0.025) to evaluate dose-response relationships. This was the primary analysis. The results of the primary analysis are shown in Table 15. Among the 4 contrasts for the primary endpoints,

14) The ALS severity classification defines severity grades from 1 to 5 (MHW Research Group for Specified Diseases [Neurodegenerative Diseases] 1998 [*Internal Medicine.* 2005; 95:1551-55]).
Grade 1: Motor dysfunction of 1 limb or dysarthria due to bulbar palsy, but no difficulty in daily living and working
Grade 2: Obvious motor dysfunction of muscles in 1 or 2 of the 6 regions of the limbs (4), the trunk (1), and the tongue/face/palate/pharynx (1) interferes with daily living, but ability to live or work unaided
Grade 3: Muscle weakness in at least 3 of the above 6 regions, and requirement of assistance in daily living due to incapability of managing social life (doing housework, working, etc.)
Grade 4: Inability to breathe, swallow, or maintain a sitting position, and requirement of constant assistance in all aspects of daily living
Grade 5: Bedridden status requiring a life support system

15) A functional rating scale developed to measure the extent to which patients with ALS are capable of performing functional activities. It is based on 12 items (speech, salivation, swallowing, handwriting, cutting food and handling utensils, dressing and hygiene, turning in bed and adjusting bed clothes, walking, climbing stairs, dyspnea, orthopnea, respiratory insufficiency), each of which is rated on a 0-4 point scale (a score of 4 represents normal function) (a maximum total score of 48).

16) The treatment period was initially 130 weeks at the start of the study, which was changed to 182 weeks because the actual annual event rate was lower than initially anticipated according to the blinded data monitoring during the study.

17) Full-time non-invasive ventilation, invasive ventilation, or death

18) For each of the log-rank test statistic for the time to event and the Wilcoxon test statistic for the change in the ALSFRS-R total score, set 2 contrasts with monotonic model [−1, 0, 1] or saturated model [−2, 1, 1], and calculate a total of 4 one-sided crude *P*-values. Then, calculate the one-sided permutation-adjusted *P*-value for each contrast. Sort the contrasts into ascending order by one-sided crude *P*-value to see if the one-sided adjusted *P*-value for the contrast with the lowest crude p-value is lower than 2.5%. The contrasts with one-sided adjusted *P*-value of <2.5% are to be declared significant. At any point, stop if the one-sided adjusted *P*-value for the contrast with the next lowest crude *P*-value is ≥2.5%.

the crude *P*-value from a test for the contrast [−2, 1, 1] using the Wilcoxon score for the change in the ALSFRS-R total score from the end of the run-in period to the last time point was the lowest (*P* = 0.087, one-sided), but the corresponding adjusted *P*-value was *P* = 0.187 (one-sided), showing no dose response.

Table 15. Time to event and the change in ALSFRS-R total score at the last time point in Japanese Study 761 (FAS, LOCF)

Treatment group	Number of subjects evaluated	Time to event[a)]	*P*-value from test for contrast using the logrank score [c)]		Change in ALSFRS-R total score from the end of run-in period to the last time point[b)]	*P*-value from test for contrast using the Wilcoxon score[c)]	
			Monotonic	Saturated		Monotonic	Saturated
Placebo	123	880 (465, −)	0.330 (0.148)	0.204 (0.126)	-21.9 ± 10.3	0.150 (0.184)	0.087 (0.187)
Mecobalamin 25 mg	124	1147 (499, −)			-20.9 ± 11.1		
Mecobalamin 50 mg	123[d)]	954 (503, −)			-19.6 ± 10.4		

a) Median (25%tile, 75%tile); −, Not calculable
b) Mean ± SD
c) One-sided crude *P*-value (One-sided permutation-adjusted *P*-value)
d) The change in the ALSFRS-R total score was calculated for 122 subjects.

Regarding safety, all adverse events[19)] and adverse events reported by ≥10% of subjects in any group are shown in Table 16.

19) Except for events leading to death, events considered by the safety assessor (the investigator) as worsening of symptoms associated with progression of the primary disease (including tracheostomy, non-invasive ventilation, invasive ventilation, subjective symptoms related to decreased respiratory function, and gastrostomy) were not to be handled as adverse events.

Table 16. All adverse events and adverse events reported by ≥10% of subjects in any group (safety analysis set)

	Placebo (N = 123)	Mecobalamin 25 mg (N = 124)	Mecobalamin 50 mg (N = 123)
Any adverse event	122 (99.2)	121 (97.6)	121 (98.4)
Adverse events reported by ≥10% of subjects in any group			
Constipation	79 (64.2)	65 (52.4)	67 (54.5)
Fall	77 (62.6)	64 (51.6)	65 (52.8)
Nasopharyngitis	50 (40.7)	57 (46.0)	49 (39.8)
Contusion	46 (37.4)	50 (40.3)	47 (38.2)
Insomnia	40 (32.5)	37 (29.8)	39 (31.7)
Diarrhoea	28 (22.8)	30 (24.2)	28 (22.8)
Respiratory failure	26 (21.1)	17 (13.7)	26 (21.1)
Erythema	14 (11.4)	17 (13.7)	22 (17.9)
Eczema	13 (10.6)	25 (20.2)	21 (17.1)
Application site pain	22 (17.9)	21 (16.9)	20 (16.3)
Pain	23 (18.7)	22 (17.7)	19 (15.4)
Pneumonia aspiration	17 (13.8)	20 (16.1)	19 (15.4)
Pneumonia	18 (14.6)	18 (14.5)	19 (15.4)
Pruritus	16 (13.0)	13 (10.5)	15 (12.2)
Excessive granulation tissue	14 (11.4)	12 (9.7)	15 (12.2)
Bronchitis	12 (9.8)	14 (11.3)	14 (11.4)
Anaemia	9 (7.3)	14 (11.3)	14 (11.4)
Back pain	22 (17.9)	22 (17.7)	13 (10.6)
Post procedural complication	17 (13.8)	19 (15.3)	13 (10.6)
Hepatic function abnormal	11 (8.9)	14 (11.3)	13 (10.6)
Upper respiratory tract inflammation	14 (11.4)	11 (8.9)	13 (10.6)
Pain in extremity	14 (11.4)	18 (14.5)	12 (9.8)
Glucose urine present	18 (14.6)	14 (11.3)	12 (9.8)
Headache	16 (13.0)	10 (8.1)	12 (9.8)
Myalgia	13 (10.6)	8 (6.5)	12 (9.8)
Arthralgia	13 (10.6)	21 (16.9)	10 (8.1)
Laceration	5 (4.1)	14 (11.3)	10 (8.1)
Decubitus ulcer	11 (8.9)	14 (11.3)	10 (8.1)
Malnutrition	16 (13.0)	9 (7.3)	10 (8.1)
Dehydration	16 (13.0)	9 (7.3)	8 (6.5)
Musculoskeletal pain	14 (11.4)	14 (11.3)	7 (5.7)
Dizziness	13 (10.6)	7 (5.6)	7 (5.7)
Abrasion	16 (13.0)	10 (8.1)	6 (4.9)
Tinea pedis	10 (8.1)	18 (14.5)	5 (4.1)

n (%)

There were 94 deaths (33 subjects in the placebo group [respiratory failure (26 subjects); and pneumonia; superior mesenteric artery syndrome and pneumonia aspiration; pneumonia aspiration; cardio-respiratory arrest; death; bile duct cancer; and acute respiratory failure (1 subject each)], 27 subjects in the mecobalamin 25 mg group [respiratory failure (14 subjects); acute respiratory failure (3 subjects); pneumonia (2 subjects); and pneumonia, atelectasis, and respiratory failure; hypercapnia; ventricular fibrillation; chronic respiratory failure; oesophageal carcinoma; spinal column injury; pneumonia aspiration; and hypothermia (1 subject each)], 34 subjects in the mecobalamin 50 mg group [respiratory failure (24 subjects); acute respiratory failure (3 subjects); pneumonia (2 subjects); and cardiac failure acute; sepsis; cardiac arrest; completed suicide; and pneumonia and respiratory failure (1 subject each)]), and a causal relationship to study drug was ruled out except for 1 case of cardiac arrest in the mecobalamin 50 mg group. Table 17 shows serious adverse events other than deaths, and a causal relationship to study drug was ruled out for all those events. The incidences of adverse events leading to treatment discontinuation were 4.9% (6 of 123 subjects) (gastric cancer; bile duct cancer; colon cancer; respiratory failure; drug eruption; and allergic dermatitis [1 subject each]) in the placebo group, 3.2% (4 of 124 subjects) (drug eruption [2 subjects]; and breast cancer; and oesophageal carcinoma [1

subject each]) in the mecobalamin 25 mg group, and 0.8% (1 of 123 subjects) (gastric cancer [1 subject]) in the mecobalamin 50 mg group, and a causal relationship to study drug was ruled out except for 1 case of allergic dermatitis in the placebo group.

Table 17. Serious adverse events other than deaths (Safety analysis set)

Placebo 48.8% (60 of 123 subjects)	Pneumonia (6 subjects); pneumonia aspiration (5 subjects); bronchitis (3 subjects); device malfunction (2 subjects); calculus ureteric (2 subjects); humerus fracture (2 subjects); cataract (2 subjects); and back pain and pneumonia; upper respiratory tract inflammation; vocal cord disorder; pneumonia and pneumonia aspiration; wound and bronchopneumonia; stress cardiomyopathy; enterocolitis; contusion, insomnia, urinary tract infection, and back pain; pneumonia and bacterial infection; colon cancer; pulmonary embolism; spinal compression fracture and dehydration; gastric cancer; sleep apnoea syndrome; pneumonia aspiration and pneumothorax; cardio-respiratory arrest and hypoxic-ischaemic encephalopathy; dehydration; colitis ulcerative; pneumonia and pyelonephritis; pneumonia and gastric ulcer haemorrhage; lower limb fracture; dehydration and gastrointestinal disorder; sputum retention; haemothorax and pneumonia aspiration; pneumonia aspiration, malnutrition, and generalised oedema; contusion; device malfunction and pneumonia; pneumonia and urinary retention; bronchopneumonia; gastroenteritis viral; headache, subdural haematoma, and pneumonia; excessive granulation tissue; autoimmune hepatitis and pneumonia aspiration; traumatic intracranial haemorrhage; pneumonia aspiration, septic shock, and cholecystitis acute; subarachnoid haemorrhage; vertigo positional and angina pectoris; and hyponatraemia (1 subject each)
Mecobalamin 25 mg 51.6% (64 of 124 subjects)	Pneumonia aspiration (7 subjects); pneumonia (7 subjects); bronchitis (3 subjects); calculus urinary (2 subjects); upper respiratory tract inflammation (2 subjects); and urinary tract infection and pneumonia; vertigo positional; cystitis noninfective; influenza; pneumonia aspiration, dehydration, upper respiratory tract inflammation, and pneumonia aspiration; blood glucose decreased; injury; foreign body; diarrhoea; diabetes mellitus; pneumonia aspiration and pneumonia; bile duct stone; laceration; pneumonia and duodenal ulcer; lower gastrointestinal haemorrhage; hypoxia, pneumonia aspiration, diarrhoea, and pneumonia; breast cancer; pneumonia and pneumonia aspiration; urinary tract infection and diverticulum intestinal haemorrhagic; femur fracture; dyspnoea and pneumonia aspiration; urinary tract infection; atelectasis and pneumonia aspiration; obstructive airways disorder; pneumonia aspiration and urinary retention; renal impairment; pneumonia and dehydration; respiratory failure; myocardial infarction; cognitive disorder; pneumonia aspiration and respiratory failure; hepatic function abnormal; urinary tract infection, electrolyte imbalance, and pneumonia aspiration; cervical vertebral fracture and volvulus; subarachnoid haemorrhage, cerebral haemorrhage, pneumothorax, haemothorax, cervical vertebral fracture, and intervertebral disc protrusion; vertigo positional and spinal compression fracture; humerus fracture; bronchitis, pneumothorax, and bronchopneumonia; dehydration; contusion; fractured sacrum, foot fracture, pharyngitis, and bronchitis; upper limb fracture; and gastroenteritis (1 subject each)
Mecobalamin 50 mg 48.9% (60 of 123 subjects)	Pneumonia aspiration (9 subjects); pneumonia (8 subjects); contusion (2 subjects); and cholecystitis; appendicitis and pneumonia; upper respiratory tract inflammation, vertigo, and acute respiratory distress syndrome; nasopharyngitis and gastric cancer; ligament injury and ligament sprain; appendicitis perforated and altered state of consciousness; pneumonia aspiration, dyspnoea, and bronchitis; cholangitis; abdominal wall haematoma, tachycardia paroxysmal, and pneumonia aspiration; hypercapnia and obstructive airways disorder; humerus fracture; constipation; gastroenteritis; pyelonephritis; renal impairment; injury and pneumonia; circulatory collapse; bronchitis and sputum retention; bronchitis; decreased appetite; brain contusion; vertigo; pneumonia aspiration and pneumonia; white blood cell count increased and pneumonia aspiration; dizziness; herpes zoster; acute respiratory failure and pneumonia aspiration; fractured skull depressed and pneumonia aspiration; muscle twitching; pneumonia aspiration and bronchopneumonia; sleep apnoea syndrome and large intestine polyp; gastric ulcer haemorrhage; gout, haemorrhoids, pneumonia aspiration, and pyelonephritis; urinary tract infection and respiratory failure; periodontitis and nephrotic syndrome; cerebral haemorrhage and ankle fracture; cataract; bronchopneumonia and dehydration; diabetes mellitus and pneumonia; sciatica and pneumonia; and supraventricular tachycardia (1 subject each)

7.3 Japanese long-term extension study (CTD 5.3.5.2.1 to 5.3.5.2.4, Study E0302-J081-762 [[redacted] to [redacted]])

An open-label, uncontrolled study was conducted to evaluate the long-term safety and efficacy of mecobalamin in subjects who completed the Japanese phase II/III study (Japanese Study 761)[20] (target sample size, up to 300 subjects).

Mecobalamin 50 mg[21] was to be administered intramuscularly twice weekly.

Among 149 enrolled subjects (47 subjects in the placebo/mecobalamin 50 mg group, 53 subjects in the mecobalamin 25 mg/mecobalamin 50 mg group, 49 subjects in the mecobalamin 50 mg/mecobalamin 50 mg

20) Subjects who completed the study were defined as subjects who completed the treatment period or required full-time non-invasive ventilation or invasive ventilation in Japanese Study 761. Those subjects were enrolled, regardless of ALS severity or %FVC at enrollment.
21) Dose reduction to 25 mg was permitted if considered necessary by the investigator etc. from safety and efficacy standpoints.

group, the same order applies hereinafter), 147 subjects (45 subjects, 53 subjects, 49 subjects) after excluding 2 subjects who did not receive study drug (2 subjects, 0 subjects, 0 subjects) were included in the efficacy and safety analysis sets, but disposal of source documents retained at the medical institution by mistake was later confirmed for 3 subjects (1 subject, 2 subjects, 0 subjects). Thus, 144 subjects (44 subjects, 51 subjects, 49 subjects) after excluding these 3 subjects were evaluated for efficacy and safety. There were 106 discontinuations up to the last time point (31 subjects, 36 subjects, 39 subjects), and the main reasons for discontinuations were the subject's refusal to continue participation in the clinical study (24 subjects [7 subjects, 11 subjects, 6 subjects]), the decision by the investigator etc. (12 subjects [4 subjects, 2 subjects, 6 subjects]), etc.

Regarding efficacy, the change from baseline in the ALSFRS-R total score, survival rate, and cumulative event[17] rate are shown in Table 18.

Table 18. Change in ALSFRS-R total score, survival rate, and cumulative event rate in Japanese Study 762 (efficacy analysis set[a])

	Week 0	Week 4	Week 16	Week 28	Week 40	Week 52	Last assessment (Week 52)
Number of subjects evaluated[b]	144	141	133	122	106	101	143
ALSFRS-R total score[c, d]	13.0 (0, 48)	12.0 (0, 48)	12.0 (0, 48)	11.5 (0, 48)	10.5 (0, 47)	9.0 (0, 47)	9.0 [f] (0, 47)
Change in ALSFRS-R total score[c]		0.0 (-17, 2)	0.0 (-17, 3)	-1.0 (-17, 1)	-1.0 (-17, 0)	-2.0 (-17, 0)	-1.0 [f] (-17, 3)
Survival rate[e, g] [95% CI]		99.3 [97.9, 100]	95.8 [92.4, 99.1]	92.9 [88.6, 97.1]	87.4 [81.7, 93.0]	85.7 [79.7, 91.7]	
Cumulative event rate[e, g] [95% CI]		0.0 [0.0, 0.0]	4.9 [0.2, 9.6]	7.5 [1.7, 13.2]	14.5 [6.5, 22.4]	20.6 [h] [11.2, 30.0]	

a) Three subjects for whom source documents were disposed of by mistake are excluded.
b) Number of subjects evaluated for ALSFRS-R total score and change in ALSFRS-R total score
c) Median (Min., Max.)
d) Week 0 represents baseline (i.e., before treatment initiation).
e) Week 0 represents the time of enrollment in Japanese Study 762.
f) Last observed data at a specified time point up to Week 52 (LOCF)
g) Estimated using the Kaplan-Meier method. Confidence intervals were calculated using Greenwood's formula.
h) Subjects who discontinued or died after Week 54 or continued through the cutoff date after Week 54 were censored at Week 52 (the last assessment).

Regarding safety, all adverse events and adverse events reported by ≥10% of subjects in any group through Week 52 (the last assessment) are shown in Table 19.

Table 19. All adverse events and adverse events reported by ≥10% of subjects in any group (safety analysis set[a])

	Placebo/Mecobalamin 50 mg (N = 44)	Mecobalamin 25 mg/ Mecobalamin 50 mg (N = 51)	Mecobalamin 50 mg/ Mecobalamin 50 mg (N = 49)
Any adverse event	42 (95.5)	48 (94.1)	46 (93.9)
Adverse events reported by ≥10% of subjects in any group			
Pruritus	1 (2.3)	4 (7.8)	7 (14.3)
Insomnia	2 (4.5)	5 (9.8)	6 (12.2)
Hepatic function abnormal	2 (4.5)	4 (7.8)	6 (12.2)
Conjunctivitis	5 (11.4)	3 (5.9)	6 (12.2)
Urinary tract infection	4 (9.1)	1 (2.0)	6 (12.2)
Nasopharyngitis	12 (27.3)	9 (17.6)	5 (10.2)
Eczema	6 (13.6)	7 (13.7)	5 (10.2)
Diarrhoea	5 (11.4)	7 (13.7)	5 (10.2)
Pyrexia	3 (6.8)	7 (13.7)	5 (10.2)
Excessive granulation tissue	3 (6.8)	6 (11.8)	5 (10.2)
Dermatitis contact	3 (6.8)	5 (9.8)	5 (10.2)
Erythema	6 (13.6)	4 (7.8)	5 (10.2)
Tinea pedis	4 (9.1)	4 (7.8)	5 (10.2)
Cystitis	3 (6.8)	2 (3.9)	5 (10.2)
Tracheostomy malfunction	2 (4.5)	0	5 (10.2)
Constipation	6 (13.6)	13 (25.5)	4 (8.2)
Pneumonia	3 (6.8)	9 (17.6)	4 (8.2)
Decubitus ulcer	2 (4.5)	6 (11.8)	4 (8.2)
Fall	7 (15.9)	6 (11.8)	3 (6.1)
Bronchitis	5 (11.4)	7 (13.7)	3 (6.1)
Respiratory failure	4 (9.1)	6 (11.8)	3 (6.1)
Contusion	5 (11.4)	4 (7.8)	3 (6.1)
Rhinitis allergic	5 (11.4)	0	2 (4.1)

n (%)

a) Three subjects for whom source documents were disposed of by mistake are excluded.

Through the last time point (study period, 3340 days), there were 43 deaths (15 subjects [respiratory failure (9 subjects); pneumonia aspiration (2 subjects); and myocardial infarction; infectious pleural effusion, sepsis, and renal failure; lung neoplasm malignant; and acute respiratory failure (1 subject each)], 17 subjects [respiratory failure (9 subjects); and cardiac failure; stress cardiomyopathy and sepsis; hypercapnia; respiratory arrest; cardiac arrest; cardio-respiratory arrest; arrhythmia; and lower respiratory tract inflammation (1 subject each)], 11 subjects [respiratory failure (5 subjects); hypoxic-ischaemic encephalopathy (2 subjects); and accidental death; pulmonary embolism; respiratory arrest; and respiratory tract infection (1 subject each)]), and a causal relationship to study drug was ruled out for all those events. Table 20 shows serious adverse events other than deaths, and a causal relationship to study drug was ruled out except for calculus urinary (1 subject) in the mecobalamin 50 mg/mecobalamin 50 mg group. The incidences of adverse events leading to treatment discontinuation were 4.5% (2 of 44 subjects [bile duct cancer; and pancreatic carcinoma (1 subject each)]) in the placebo/mecobalamin 50 mg group, 2.0% (1 of 51 subjects [colon cancer (1 subject]) in the mecobalamin 25 mg/mecobalamin 50 mg group, and 6.1% (3 of 49 subjects [dyspnoea; gastric cancer; and convulsion (1 subject each)]) in the mecobalamin 50 mg/mecobalamin 50 mg group, but a causal relationship to study drug was ruled out for all those events.

Table 20. Serious adverse events other than deaths (safety analysis set[a])

Placebo/Mecobalamin 50 mg 61.4% (27 of 44 subjects)	Pneumonia aspiration (2 subjects); bronchopneumonia (2 subjects); and pneumonia and bile duct cancer; psoas abscess; hyponatraemia and otitis media acute; pyrexia; tracheobronchitis mycoplasmal; pneumonia and accidental exposure to product; rib fracture; sleep apnoea syndrome and bronchitis; nasopharyngitis, pneumonia aspiration, abdominal pain upper, and respiratory tract infection; pancreatic carcinoma; gastrointestinal hypomotility; application site pain; application site haemorrhage, stress cardiomyopathy, and hyponatraemia; malnutrition, generalised oedema, and liver injury; intestinal obstruction and pneumonia aspiration; respiratory failure; peripheral artery thrombosis, cholecystitis, disseminated intravascular coagulation, septic shock, and sepsis; upper gastrointestinal haemorrhage; pneumonia; excessive granulation tissue; autoimmune hepatitis, pneumonia aspiration, and cholangitis; hand fracture; and post procedural haemorrhage and respiratory failure (1 subject each)
Mecobalamin 25 mg/Mecobalamin 50 mg 51.0% (26 of 51 subjects)	Pneumonia (3 subjects); and pneumonia, pyrexia, calculus bladder, and abdominal pain; skull fracture and subarachnoid haemorrhage; spinal osteoarthritis; pneumonia, cholecystitis, atelectasis, intestinal obstruction, and arrhythmia; jaundice cholestatic; pneumonia and anaemia; respiratory failure; pulmonary embolism and bronchitis; pneumomediastinum; respiratory tract infection, bronchitis, dehydration, cholelithiasis, and cellulitis; pneumonia aspiration; laceration, peritonitis, volvulus, and constipation; decreased appetite and pneumonia aspiration; hepatic function abnormal, pneumonia, cholecystitis, and pneumothorax; cholecystitis acute; urinary retention, cholelithiasis, haemorrhoids, colon cancer, and device malfunction; pneumonia, pneumothorax, cholecystitis acute, bile duct stone, mesenteric panniculitis, and cholangitis; myocardial infarction, angina pectoris, pancytopenia, and pneumonia; diverticulum intestinal haemorrhagic, pneumonia aspiration, colitis ischaemic, and large intestinal haemorrhage; pyrexia; spinal compression fracture, femur fracture, fracture, tibia fracture, and vertigo positional; bronchitis; and vertigo positional, dyspnoea, bronchitis, pneumonia, and vertigo positional (1 subject each)
Mecobalamin 50 mg/Mecobalamin 50 mg 67.3% (33 of 49 subjects)	Pneumonia aspiration (2 subjects); and cholelithiasis, pneumonia, seborrhoeic dermatitis, and atelectasis; cellulitis, pyrexia, pneumonia, and ileus paralytic; pyrexia; pneumonia aspiration, atelectasis, cholecystitis acute, lobar pneumonia, bacterial infection, and shock; blood pressure decreased; pneumonia, cellulitis, pneumonia aspiration, amylase increased, pancreatitis acute, and cholelithiasis; device malfunction and tracheo-oesophageal fistula; hepatic function abnormal, atelectasis, and pneumonia aspiration; pneumonia aspiration, oliguria, malnutrition, cellulitis, pyelonephritis, and intestinal obstruction; enteritis infectious, hyperkalaemia, and cerebral infarction; pneumonia aspiration, dyspnoea, and chest discomfort; cellulitis, pneumonia, urinary tract infection, sepsis, septic shock, disseminated intravascular coagulation, and cerebral infarction; sepsis; respiratory tract infection, duodenal ulcer, and cerebral infarction; pneumonia; pyelonephritis, pneumonia, and staphylococcal infection; dyspnoea; pneumonia and dehydration; cystitis; calculus urinary, pyelonephritis, and urinary tract infection; cerebral infarction, dizziness postural, spinal osteoarthritis, diabetes mellitus, gastric cancer, cholecystitis, and cataract; pneumonia, bronchitis, bronchopneumonia, cholangitis, ileus paralytic, pneumonia, sepsis, and convulsion; sleep apnoea syndrome and large intestine polyp; femoral neck fracture, ileus paralytic, and pneumonia aspiration; volvulus, superior mesenteric artery syndrome, device malfunction, and altered state of consciousness; periodontitis, nephrotic syndrome, nasopharyngitis, pneumonia aspiration, and application site abscess; pneumothorax, excessive granulation tissue, and pneumonia; dyspnoea, pneumonia aspiration, and pseudomembranous colitis; humerus fracture; dysuria, haematuria, and inguinal hernia; and pulmonary artery thrombosis (1 subject each)

a) Three subjects for whom source documents were disposed of by mistake are excluded.

7.4 Japanese phase III study (CTD 5.3.5.1.2 and 5.3.5.1.3, Study E0302-TOK-763 [ongoing since November 2017 (■ 20■ data cutoff, ■ 20■ additional data cutoff)])

A clinical study was conducted to evaluate the efficacy and safety of mecobalamin in Japanese patients with ALS aged ≥20 years (target sample size, 128 subjects [64 per group[22)]]). The study consisted of a run-in phase (12 weeks), a treatment phase (a placebo-controlled, randomized, double-blind, parallel-group phase, 16 weeks), and an extension phase (an open-label, uncontrolled phase).

The key inclusion criteria for the treatment phase: "definite," "probable," or "probable-laboratory supported" ALS according to the updated Awaji criteria[23)]; grade 1 or 2 of the ALS severity classification; %FVC >60%;

22) Assuming mean changes in the ALSFRS-R total score at Week 16 of −3.2 in the mecobalamin 50 mg group and −5.8 in the placebo group, a treatment difference of 2.6, and a standard deviation of 5.0 based on the results of a previous clinical study, a sample size of 60 subjects per group would provide ≥80% power at a one-sided significance level of 0.025 to detect the difference between the mecobalamin and placebo groups. Allowing for discontinuations, a target sample size of 64 subjects per group was chosen.

23) In Japanese Study 763, patients were classified into the following 4 levels of diagnostic certainty based on the updated Awaji criteria.
1. Definite: Clinical or electrophysiological evidence by the presence of upper motor neuron and lower motor neuron signs in the bulbar region and 2 spinal regions or the presence of upper motor neuron and lower motor neuron signs in 3 spinal regions
2. Probable: Clinical or electrophysiological evidence by upper motor neuron and lower motor neuron signs in 2 regions with some upper motor neuron signs necessarily rostral to the lower motor neuron signs
3. Probable-laboratory supported: Clinical signs of upper motor neuron and lower motor neuron dysfunction in 1 region, or upper motor neuron signs in 1 region, and electrophysiological signs of lower motor neuron loss in 2 regions
4. Possible: Clinical or electrophysiological sings of upper motor neuron and lower motor neuron dysfunction in 1 region or upper motor neuron signs alone in ≥2 regions or lower motor neuron signs rostral to upper motor neuron signs in 1 region

≤1 year since ALS symptom onset; and a 1-point to 2-point decline in the ALSFRS-R total score over the run-in period.

During the treatment period, placebo or mecobalamin 50 mg was to be administered intramuscularly twice weekly for 16 weeks. Patients who wished to continue treatment with mecobalamin were allowed to enter the extension phase. During the extension period, mecobalamin 50 mg was to be administered intramuscularly twice weekly.

Subjects were randomized into the treatment period using a dynamic allocation procedure stratifying for onset type (bulbar or upper or lower limb onset), ALS severity at the end of the run-in period (grade 1 or 2), the time from symptom onset to the start of the run-in period (≤9 months or >9 months and ≤12 months), %FVC at the end of the run-in period (<90% or ≥90%), and prior treatment with edaravone (yes, no). Subjects were randomized in a 1:1 ratio to receive either placebo or mecobalamin.

(1) Treatment period

Among 130 randomized subjects (65 subjects in the placebo group, 65 subjects in the mecobalamin 50 mg group, the same order applies hereinafter), 129 subjects (64 subjects, 65 subjects) were included in the safety analysis set and in the FAS, and the FAS was used as the efficacy analysis set. The remaining 1 subject (1 in the placebo group) was excluded from the analyses because of ineligibility for the study. There were 3 discontinuations (1 subject, 2 subjects), and the reasons for discontinuations were all patient request.

Table 21 shows the primary endpoint of the change in the ALSFRS-R total score from the end of the run-in period to Week 16 of the treatment period. There was a statistically significant difference between the mecobalamin and placebo groups.

Table 21. Change in ALSFRS-R total score from the end of run-in period to Week 16 of treatment period in Japanese Study 763 (FAS)

	Number of subjects evaluated	Change [95% CI] [a)]	Treatment difference in change [95% CI] [a)]	*P*-value [b)]
Placebo	63	-4.6 [-5.8, -3.4]		
Mecobalamin 50 mg	63	-2.7 [-3.9, -1.5]	2.0 [0.4, 3.5]	0.012

a) Calculated using a mixed-effect model with total score at the end of the run-in period as a covariate, onset type, ALS severity at the end of the run-in period, the time from symptom onset to the start of the run-in period, %FVC at the end of the run-in period, prior treatment with edaravone, treatment, time, and time-by-treatment interaction as fixed effects, and subject as a random effect. The Kenward-Roger method was used to adjust degrees of freedom, and an unstructured covariance structure was used.
b) A two-sided significance level of 5%

Regarding safety, all adverse events and adverse events reported by ≥5% of subjects in either group are shown in Table 22.

Table 22. All adverse events and adverse events reported by ≥5% of subjects in either group (safety analysis set)

	Placebo (N = 64)	Mecobalamin 50 mg (N = 65)
Any adverse event	42 (65.6)	40 (61.5)
Adverse events reported by ≥5% of subjects in either group		
Contusion	7 (10.9)	5 (7.7)
Nasopharyngitis	7 (10.9)	4 (6.2)
Fall	2 (3.1)	4 (6.2)
Hepatic function abnormal	0	4 (6.2)
Constipation	4 (6.3)	3 (4.6)
Back pain	4 (6.3)	3 (4.6)
Insomnia	4 (6.3)	1 (1.5)

n (%)

No deaths were reported. Serious adverse events occurred in 2 subjects in the placebo group (cerebral infarction [1 subject] and tracheal stenosis [1 subject]) and 1 subject in the mecobalamin 50 mg group (haemorrhoid operation), but a causal relationship to study drug was ruled out for all those events. No adverse events leading to treatment discontinuation were reported.

(2) Entire period (Treatment and extension periods)

Among overall subjects, 125 subjects (62 subjects in the placebo/mecobalamin 50 mg group, 63 subjects in the mecobalamin 50 mg/mecobalamin 50 mg group, the same order applies hereinafter) entered the extension phase, but 5 subjects (3 subjects in the placebo group, 2 subjects in the mecobalamin 50 mg group) did not. Among 130 subjects randomized into the treatment period, 129 subjects (64 subjects, 65 subjects) were included in the FAS in the entire period. The FAS was used as the efficacy analysis set, and 129 subjects (64 subjects, 65 subjects) were included in the safety analysis set in the entire period. During the extension period ([redacted] data cutoff), there were 112 discontinuations (57 subjects, 55 subjects), and the main reasons for discontinuations were the subject's refusal to continue participation in the clinical study (35 subjects [16 subjects, 19 subjects]), decision by the investigator etc. (21 subjects [11 subjects, 10 subjects]), etc.

Regarding efficacy, the mean ALSFRS-R total score over time and the cumulative event rate during the entire period (Treatment and extension periods [[redacted] data cutoff]) are shown in Table 27 and Figure 2, respectively [see Section 7.R.2].

Regarding safety, the duration of study drug exposure (days [mean ± SD] and patient-years) during the entire period (Treatment and extension periods [[redacted] data cutoff]) was 634.5 ± 420.7 days and 187.5 patient-years. All adverse events and adverse events reported by ≥5% of subjects in either group are shown in Table 23.

Table 23. All adverse events and adverse events reported by ≥5% of subjects in either group (safety analysis set)

	Placebo/Mecobalamin 50 mg (N = 64)	Mecobalamin 50 mg/ Mecobalamin 50 mg (N = 65)
Any adverse event	61 (95.3)	59 (90.8)
Adverse events reported by ≥5% of subjects in either group		
Constipation	20 (31.3)	18 (27.7)
Contusion	15 (23.4)	15 (23.1)
Nasopharyngitis	15 (23.4)	13 (20.0)
Fall	6 (9.4)	11 (16.9)
Back pain	9 (14.1)	9 (13.8)
Insomnia	13 (20.3)	8 (12.3)
Stomatitis	6 (9.4)	7 (10.8)
Respiratory failure	6 (9.4)	6 (9.2)
Rash	4 (6.3)	6 (9.2)
Pruritus	9 (14.1)	5 (7.7)
Wound complication	7 (10.9)	5 (7.7)
Hepatic function abnormal	2 (3.1)	5 (7.7)
Bronchitis	3 (4.7)	5 (7.7)
Musculoskeletal pain	2 (3.1)	5 (7.7)
Pharyngitis	0	5 (7.7)
Glucose urine present	0	5 (7.7)
Pneumonia aspiration	8 (12.5)	4 (6.2)
Diarrhoea	5 (7.8)	4 (6.2)
Pneumonia	4 (6.3)	4 (6.2)
Decubitus ulcer	2 (3.1)	4 (6.2)
Myalgia	1 (1.6)	4 (6.2)
Dizziness	7 (10.9)	3 (4.6)
Dry skin	4 (6.3)	3 (4.6)
Skin abrasion	4 (6.3)	3 (4.6)
Arthralgia	6 (9.4)	3 (4.6)
Eczema	8 (12.5)	2 (3.1)
Catheter site pain	4 (6.3)	2 (3.1)
Seborrhoeic dermatitis	5 (7.8)	0
Erythema	4 (6.3)	0
Rhinitis allergic	4 (6.3)	0

n (%)

During the entire period (Treatment and extension periods [[redacted] 20[redacted] data cutoff]), there were 11 deaths (respiratory failure [6 subjects]; pneumonia aspiration [2 subjects]; and asphyxia; cardiac arrest; and pneumonia [1 subject each]) in the placebo/mecobalamin 50 mg group and 10 deaths[24)] (respiratory failure [4 subjects]; and cardiac arrest; pneumonia; hypercapnia; bronchitis; asphyxia; and pneumonia aspiration [1 subject each]) in the mecobalamin 50 mg/mecobalamin 50 mg group, and a causal relationship to study drug was ruled out for all those events. Table 24 shows serious adverse events other than deaths during the entire period (Treatment and extension periods [[redacted] 20[redacted] data cutoff]), and a causal relationship to study drug was ruled out for all those events.

The incidences of adverse events leading to treatment discontinuation were 18.8% (12 of 64 subjects [respiratory failure (4 subjects); pneumonia aspiration (3 subjects); and pneumonia and asphyxia; cardiac arrest; hyperglycaemia and urobilinogen urine increased; pneumonia; and ileus, sinusitis, and respiratory failure (1 subject each)]) in the placebo/mecobalamin 50 mg group and 10.8% (7 of 65 subjects [respiratory failure (3 subjects); hypercapnia (2 subjects); and pneumonia aspiration; and asphyxia (1 subject each)]) in the mecobalamin 50 mg/mecobalamin 50 mg group, and a causal relationship to study drug was ruled out for all those events.

24) Pneumonia aspiration occurred after cessation of study treatment.

Table 24. Serious adverse events other than deaths

Placebo/Mecobalamin 50 mg 32.8% (21 of 64 subjects)	Pneumonia aspiration (3 subjects); pneumonia (2 subjects); and calculus urethral[a)] and tracheal stenosis; pulmonary embolism and pneumonia aspiration; cardiac arrest; haemorrhoids; device related infection; hypersensitivity; fibula fracture and pneumonia aspiration; bronchitis; back pain; subarachnoid haemorrhage; catheter site pain; enterocolitis and lung neoplasm malignant; cerebral infarction and pneumonia; nephrolithiasis, infectious pleural effusion, and haematoma muscle; femoral neck fracture; and ileus (1 subject each)
Mecobalamin 50 mg/Mecobalamin 50 mg 33.8% (22 of 65 subjects)	Pneumonia aspiration (3 subjects); and sudden hearing loss[a)]; peritonitis; abdominal distension; pneumonia; decreased appetite and respiratory failure; spinal compression fracture; hypercapnia; haemorrhoid operation; cataract operation and eye complication associated with device; respiratory failure; pyrexia; haemorrhoids and large intestine polyp; pneumonia aspiration and catheter site infection; cataract; asthma and infection; coronavirus infection and pneumonia; heat illness and delirium; pneumonia and prinzmetal angina; and femur fracture (1 subject each)

n (%)
a) Occurred before initiation of study treatment.

7.R Outline of the review conducted by PMDA

7.R.1 Justification for study design and the strategy for efficacy evaluation

The applicant's explanation about the development plan and the clinical data package for the proposed product: A series of clinical research of mecobalamin in ALS patients, which had been conducted since the 1990s by the Research Group for Neurodegenerative Diseases of the Research Project on Specified Diseases under the Health Science Research Grants, suggested the possible clinical effect of mecobalamin 50 mg administered intramuscularly twice weekly to ALS patients. Thus, Japanese Study 761 in which mecobalamin 25 or 50 mg was administered intramuscularly twice weekly to ALS patients was conducted. The primary endpoints of the study were the time to event (full-time non-invasive ventilation, invasive ventilation, or death) and the change in the ALSFRS-R total score from the end of the run-in period to the last time point. The point estimate for time to event tended to be longer, and the point estimate for decline in the ALSFRS-R total score tended to be slower in the mecobalamin 25 mg and 50 mg groups than in the placebo group, whereas there were no statistically significant differences in either endpoint between the mecobalamin and placebo groups [see Section 7.2].

The progression of symptoms and prognosis in ALS are known to be highly variable among individual patients, and there are also multiple reports that the interval between ALS symptom onset and diagnosis is a prognostic factor (*Neurol Clin Pract*. 2013; 3: 313-20, *BMC Neurol.* 2014; 14: 197, etc.). In a subgroup of "patients who entered the study ≤12 months after ALS symptom onset" who were considered to have poor prognosis in Japanese Study 761 after excluding patients who were expected to progress slowly, the times from enrollment in the treatment phase to event (median [25th percentile, 75th percentile]) were 570 days (363 days, 925 days) in the placebo group (48 subjects), 1087 days (410 days, not calculable) in the mecobalamin 25 mg group (54 subjects), and 1197 days (448 days, not calculable) in the mecobalamin 50 mg group (42 subjects). The changes in the ALSFRS-R total score from the end of the run-in period to the last time point (mean ± SD) were −24.9 ± 9.3 in the placebo group (48 subjects), −24.9 ± 9.3 in the mecobalamin 25 mg group (54 subjects), and −19.6 ± 10.3 in the mecobalamin 50 mg group (41 subjects). As shown in the above, the prolongation of the time to event and the slowing of decline in the ALSFRS-R total score with mecobalamin compared to placebo were greater in the subgroup of patients with a disease duration from symptom onset of ≤12 months than in the overall population, and mecobalamin had acceptable safety. Given these and other findings, Japanese Study 763 in ALS patients with a disease duration from symptom onset of ≤12 months was initiated as an investigator-

initiated study. Japanese Study 763 demonstrated the superiority of mecobalamin 50 mg to placebo in the primary endpoint of the change in the ALSFRS-R total score from the end of the run-in period to Week 16 of the treatment period [see Section 7.4].

Based on the above results, the applicant concluded that Japanese Study 763 demonstrated the efficacy of mecobalamin in the treatment of ALS and decided to use the results from this study as the main study data for evaluating the efficacy of mecobalamin. The applicant also decided to evaluate the long-term efficacy and safety of mecobalamin in ALS patients, based on the results from Japanese Study 761 and its open-label extension study, Japanese Study 762, in addition to the results from Japanese Study 763.

The applicant's explanation about the study design of Japanese Study 763:

- The ALSFRS-R is a clinical measure of functional impairment (the limb motor, bulbar, and respiratory function) in ALS patients and is widely used as the primary endpoint for Japanese and foreign clinical studies in ALS patients. The change in the ALSFRS-R total score from the end of the run-in period was chosen as the primary endpoint for Japanese Study 763 (*Brain and Nerve*. 2001; 53: 346-55). As secondary endpoints, the time to event (full-time non-invasive ventilation, invasive ventilation, or death), etc., were to be evaluated.
- Week 16 of treatment was chosen as the timing of the analysis of the primary endpoint for Japanese Study 763 because the results of the analysis of a subgroup of patients with a disease duration from symptom onset of ≤12 months in Japanese Study 761 showed a trend in favor of mecobalamin compared to placebo regarding the change in the ALSFRS-R total score from the end of the run-in period to Week 16 of treatment.
- Japanese Study 763 was intended to include patients with early ALS. Thus, patients with sporadic or familial ALS diagnosed as "definite," "probable," or "probable-laboratory supported" ALS as defined by the updated Awaji criteria and a disease duration from symptom onset of ≤1 year were eligible for the study. In order to exclude patients with slow or rapid disease progression, patients with a 1-point to 2-point decline in the ALSFRS-R total score over the run-in period (12 weeks) were to be selected.
- The dosing regimen of mecobalamin 50 mg administered intramuscularly twice weekly was selected for the mecobalamin group of Japanese Study 763 because the results of the analysis of a subgroup of patients with a disease duration from symptom onset of ≤12 months in Japanese Study 761 suggested a dose response with mecobalamin 50 mg and 25 mg for the time to event and the ALSFRS-R total score.

PMDA's view:

Although Japanese Study 761 initially failed to demonstrate significant efficacy, the applicant reviewed the target population for study drug based on the results from Japanese Study 761 and then designed and conducted a new confirmatory study, Japanese Study 763, as a placebo-controlled study with the primary endpoint of the change in the ALSFRS-R total score from the end of the run-in period. This strategy is understandable. Thus, the strategy of evaluating the efficacy of mecobalamin based mainly on the results from Japanese Study 763 and the long-term efficacy and safety of mecobalamin etc. based on the results from Japanese Studies 761 and 762 in addition to Japanese Study 763 (the investigation of the long-term efficacy and safety of mecobalamin

etc. was limited in Japanese Study 763) is acceptable. However, given that Japanese Study 763 was designed to enroll "ALS patients with a disease duration from symptom onset of ≤12 months" and conducted, indication-related information, including the appropriateness of the main patient population for which mecobalamin is recommended, will be discussed in Section 7.R.4.

7.R.2 Efficacy

PMDA asked the applicant to explain the efficacy of mecobalamin.

The applicant's explanation:

Table 21 shows the primary endpoint of Japanese Study 763 of the change in the ALSFRS-R total score from the end of the run-in period to Week 16 of the treatment period. The study demonstrated the superiority of mecobalamin to placebo. Table 25 shows the changes in the secondary endpoints from the end of the run-in period to Week 16 of the treatment period, suggesting a trend towards higher efficacy in the mecobalamin group than in the placebo group, on the whole. On the other hand, the time to event (full-time non-invasive ventilation, invasive ventilation, or death) was unevaluable because no events occurred in either the mecobalamin or placebo group during the evaluation period.

Table 25. Changes in the secondary endpoints from the end of the run-in period to Week 16 of the treatment period in Japanese Study 763 (FAS)

Endpoint	Placebo		Mecobalamin 50 mg		Treatment difference [95% CI]
	N	LS Mean [95% CI]	N	LS Mean [95% CI]	
%FVC	62	-9.4 [-12.9, -5.9]	63	-7.4 [-11.0, -3.8]	2.0 [-1.9, 5.8]
Blood homocysteine concentration	63	0.0 [-0.5, 0.5]	63	-1.7 [-2.3, -1.1]	-1.7 [-2.2, -1.2]
MMT total score	63	-3.7 [-5.0, -2.4]	63	-2.9 [-4.3, -1.5]	0.8 [-0.6, 2.3]
Grip strength (right hand) (kg)	62	-2.5 [-3.9, -1.1]	63	-2.7 [-4.1, -1.2]	-0.2 [-1.6, 1.3]
Grip strength (left hand) (kg)	62	-2.5 [-3.7, -1.2]	63	-2.1 [-3.4, -0.8]	0.4 [-0.9, 1.7]
Norris scale total score	63	-9.9 [-12.9, -6.8]	63	-7.0 [-10.1, -3.8]	2.9 [-0.5, 6.3]
ALSAQ-40 total score	62	18.2 [11.2, 25.1]	63	15.4 [8.1, 22.7]	-2.8 [-10.0, 4.5]

The applicant's view on the long-term efficacy of mecobalamin based on the results from Japanese Studies 761 and 763:

The event rates in Japanese Study 761 were 17.8% at Month 21 and 19.2% at Month 26, which were lower than initially anticipated (50%-55%) at the time of designing the study. Thus, the treatment period was extended from 130 weeks (2.5 years) to 182 weeks (3.5 years) during the study. Since patients with a disease duration from ALS symptom onset of ≤3 years were enrolled in Japanese Study 761, the extension of the study period allowed for assessing the event rates at 3.5 to 6.5 years after ALS symptom onset. Given the general survival time of ALS patients, the extended study period of Japanese Study 761 was considered sufficient to evaluate the long-term efficacy of mecobalamin in ALS patients.

The cumulative event rate over time since enrollment in the treatment phase and the ALSFRS-R total score over time since the end of run-in period in Japanese Study 761 are shown in Figure 1 and Table 26, respectively. The superiority of mecobalamin 25 or 50 mg to placebo was not demonstrated in terms of the primary endpoint

of either the time to event or the change in the ALSFRS-R total score at Week 182. However, the effects of mecobalamin based on the point estimates were higher than those of placebo, suggesting the long-term efficacy of mecobalamin.

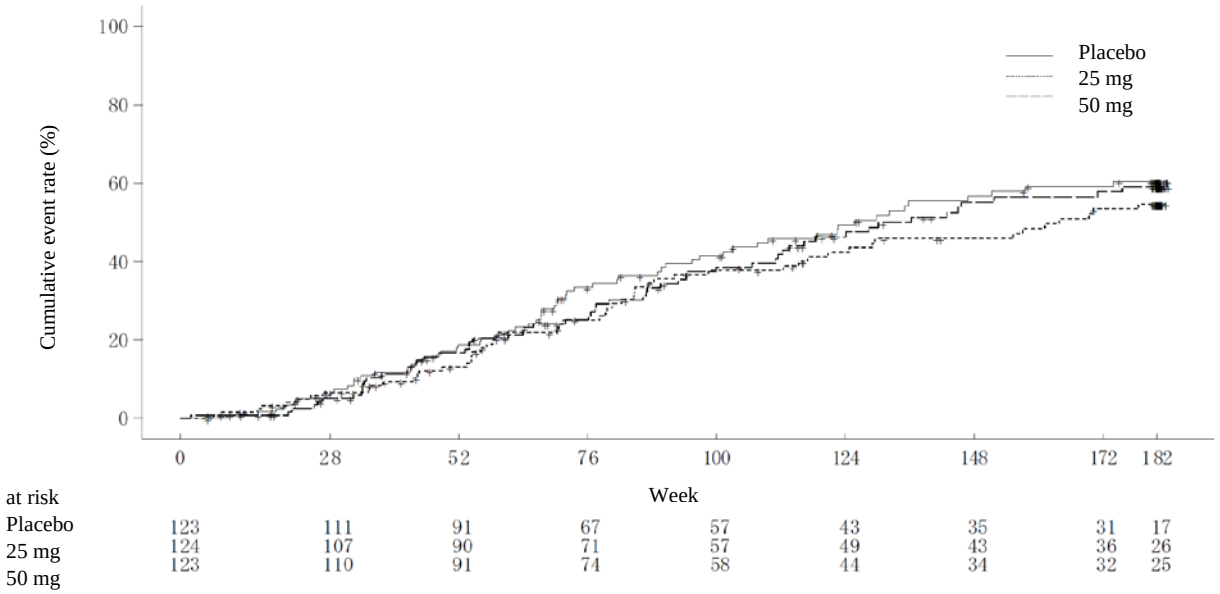

Figure 1. Cumulative event rate over time since enrollment in treatment phase in Japanese Study 761 (FAS)

Table 26. ALSFRS-R total score over time since the end of run-in period in Japanese Study 761 (FAS)

	Placebo			Mecobalamin 25 mg			Mecobalamin 50 mg		
	N	Mean	Median	N	Mean	Median	N	Mean	Median
Week 0	123	40.1 ± 3.5	41.0 (28, 47)	124	39.8 ± 4.0	40.0 (29, 47)	123	39.9 ± 4.0	40.0 (28, 47)
Week 4	122	38.3 ± 4.4	39.0 (25, 48)	123	38.0 ± 5.4	39.0 (16, 47)	120	38.7 ± 4.8	39.0 (24, 47)
Week 16	121	34.7 ± 7.6	36.0 (6, 47)	124	34.3 ± 8.6	36.0 (5, 47)	122	36.0 ± 7.0	37.5 (15, 48)
Week 28	122	31.8 ± 9.7	34.5 (4, 48)	123	31.3 ± 9.4	34.0 (5, 47)	122	33.1 ± 8.8	35.0 (6, 48)
Week 40	122	29.8 ± 10.5	32.5 (4, 48)	122	28.5 ± 10.6	31.0 (0, 47)	121	30.8 ± 9.9	33.0 (2, 48)
Week 52	123	27.5 ± 10.8	30.0 (1, 48)	124	26.3 ± 11.1	28.5 (0, 47)	122	28.5 ± 10.8	30.0 (2, 46)
Week 64	123	25.3 ± 11.2	27.0 (1, 48)	122	24.8 ± 11.5	26.5 (0, 47)	121	27.0 ± 10.9	28.0 (2, 46)
Week 76	123	23.6 ± 11.7	25.0 (1, 48)	124	23.5 ± 11.5	24.5 (0, 47)	122	25.6 ± 11.2	26.0 (2, 48)
Week 88	123	22.3 ± 11.9	23.0 (1, 48)	123	22.2 ± 11.8	22.0 (0, 47)	121	24.5 ± 11.3	25.0 (2, 48)
Week 100	123	21.0 ± 11.8	21.0 (1, 48)	123	21.6 ± 11.7	21.0 (0, 47)	122	23.5 ± 11.3	23.0 (2, 48)
Week 112	123	20.3 ± 11.6	20.0 (1, 48)	124	20.9 ± 11.8	20.5 (0, 47)	120	22.6 ± 11.3	21.5 (2, 48)
Week 124	123	19.8 ± 11.4	19.0 (1, 48)	123	20.3 ± 11.9	20.0 (0, 47)	122	22.2 ± 11.2	21.5 (1, 48)
Week 136	123	19.3 ± 11.2	18.0 (1, 48)	123	20.0 ± 11.8	20.0 (0, 47)	122	21.5 ± 11.4	20.0 (1, 48)
Week 148	123	19.1 ± 11.2	17.0 (1, 48)	124	19.6 ± 11.8	20.0 (0, 47)	122	21.1 ± 11.5	19.5 (1, 48)
Week 160	123	18.7 ± 11.1	17.0 (1, 48)	124	19.3 ± 11.9	19.5 (0, 47)	121	20.8 ± 11.4	19.0 (1, 48)
Week 172	123	18.4 ± 11.0	17.0 (1, 48)	124	19.0 ± 11.9	18.0 (0, 47)	121	20.6 ± 11.5	19.0 (1, 48)
Week 182	123	18.2 ± 11.0	16.0 (1, 48)	124	18.9 ± 11.9	17.5 (0, 47)	122	20.4 ± 11.4	19.0 (1, 48)

Mean ± SD, Median (Min., Max.)

During the entire period of Japanese Study 763 (Treatment and extension periods [[redacted] 20[redacted] data cutoff][25]), the cumulative event rate over time and the ALSFRS-R total score over time are shown in Figure 2 and Table 27, respectively. Since all subjects received active drug from Week 16 (of study treatment) onward, the results should be interpreted with care. In addition, there was large inter-individual variability, and the number of subjects analyzed was limited, especially with prolonged treatment. Thus, rigorous comparison is difficult. Nevertheless, the cumulative event rate and the ALSFRS-R total score over time following administration of mecobalamin in Japanese Study 763 were consistent with the results from Japanese Study 761 concerning the cumulative event rate and the ALSFRS-R total score.

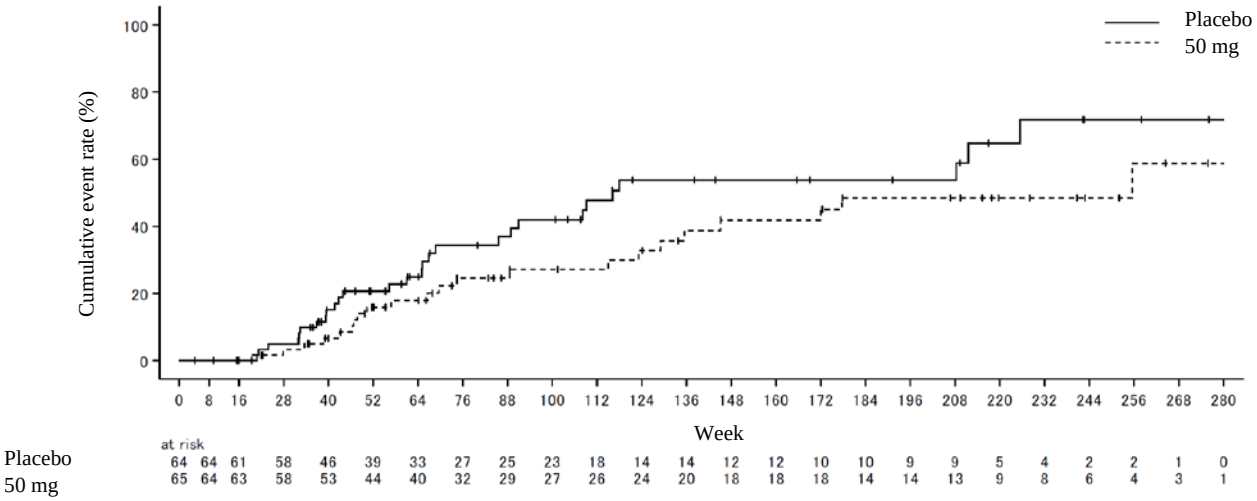

Figure 2. Cumulative event rate over time since study drug randomization in Japanese Study 763 (FAS)

Table 27. ALSFRS-R total score over time since the end of run-in period in Japanese Study 763 (FAS)

	Placebo			Mecobalamin 50 mg		
	N	Mean	Median	N	Mean	Median
Week 0	64	42.3 ± 2.7	43.0 (31.0, 46.0)	65	42.4 ± 2.6	43.0 (36.0, 47.0)
Week 4	64	40.9 ± 3.5	42.0 (32.0, 46.0)	65	42.0 ± 3.0	42.0 (33.0, 47.0)
Week 8	64	39.8 ± 4.3	41.0 (27.0, 46.0)	64	40.8 ± 3.6	42.0 (32.0, 47.0)
Week 16	63	37.5 ± 5.9	39.0 (19.0, 46.0)	63	39.3 ± 4.5	40.0 (29.0, 47.0)
Week 28	59	34.5 ± 7.6	36.0 (15.0, 46.0)	61	36.7 ± 6.3	38.0 (22.0, 47.0)
Week 40	48	32.1 ± 8.5	33.0 (13.0, 46.0)	54	34.1 ± 8.1	36.5 (16.0, 47.0)
Week 52	38	31.2 ± 8.4	32.0 (16.0, 46.0)	44	33.1 ± 8.8	35.0 (13.0, 47.0)
Week 64	34	29.4 ± 9.0	30.0 (13.0, 43.0)	39	31.7 ± 9.6	35.0 (14.0, 46.0)
Week 76	26	29.9 ± 9.1	32.5 (13.0, 43.0)	33	30.7 ± 10.5	34.0 (8.0, 46.0)
Week 88	25	28.6 ± 9.8	32.0 (10.0, 43.0)	31	28.5 ± 11.5	31.0 (8.0, 46.0)
Week 100	22	28.0 ± 9.5	31.0 (10.0, 42.0)	27	29.2 ± 11.1	31.0 (5.0, 46.0)
Week 112	17	26.3 ± 10.7	30.0 (6.0, 41.0)	26	28.3 ± 10.6	28.5 (8.0, 46.0)
Week 124	15	28.3 ± 8.3	29.0 (12.0, 41.0)	25	27.3 ± 11.4	27.0 (2.0, 46.0)
Week 136	13	27.7 ± 8.9	26.0 (12.0, 40.0)	21	28.5 ± 10.9	33.0 (8.0, 46.0)
Week 148	13	26.5 ± 9.2	26.0 (12.0, 40.0)	18	27.4 ± 11.1	29.0 (11.0, 46.0)
Week 160	12	25.2 ± 9.7	26.0 (12.0, 38.0)	18	26.9 ± 11.4	28.5 (10.0, 46.0)
Week 172	10	25.6 ± 9.6	27.5 (12.0, 38.0)	17	25.9 ± 11.3	28.0 (5.0, 46.0)
Week 184	10	24.1 ± 9.6	25.0 (12.0, 38.0)	15	27.0 ± 12.1	29.0 (2.0, 46.0)
Week 196	9	24.7 ± 9.4	26.0 (12.0, 38.0)	14	27.1 ± 11.9	28.5 (2.0, 46.0)
Week 208	8	22.9 ± 10.0	24.0 (11.0, 38.0)	13	26.2 ± 12.4	28.0 (2.0, 46.0)
Week 220	5	18.6 ± 11.9	20.0 (5.0, 32.0)	10	23.7 ± 12.1	24.5 (2.0, 39.0)
Week 232	4	20.8 ± 10.0	22.0 (8.0, 31.0)	8	22.1 ± 13.5	21.0 (2.0, 39.0)
Week 244	2	20.0 ± 15.6	20.0 (9.0, 31.0)	7	22.9 ± 13.5	22.0 (2.0, 39.0)
Week 256	2	18.0 ± 14.1	18.0 (8.0, 28.0)	5	20.8 ± 16.8	15.0 (2.0, 39.0)
Week 268	1	7.0	7.0	3	19.0 ± 18.1	17.0 (2.0, 38.0)

25) Not the cutoff data according to the formal in-house procedure.

Mean ± SD, Median (Min., Max.)
Extension period (from Week 16 onward)

Table 28 shows the results of subgroup analyses of the change in the ALSFRS-R total score from the end of the run-in period to Week 16 of the treatment period in Japanese Study 763 according to subject characteristics. Although rigorous comparison is difficult due to the limited number of subjects in some subgroups, there was no trend towards clearly different efficacy in a subgroup of patients with specific characteristics.

Table 28. Results of subgroup analyses of the change in the ALSFRS-R total score in Japanese Study 763 (FAS)

Item		Placebo		Mecobalamin 50 mg	
		N	Median	N	Median
Age	<65 years	33	-3.0 (-24.0, 1.0)	32	-2.0 (-12.0, 3.0)
	≥65 years	30	-3.0 (-15.0, 2.0)	31	-3.0 (-13.0, 2.0)
Sex	Male	39	-3.0 (-24.0, 2.0)	32	-2.0 (-7.0, 3.0)
	Female	24	-2.5 (-11.0, 1.0)	31	-3.0 (-13.0, 2.0)
BMI	<18.5 kg/m^2	8	-4.5 (-10.0, 1.0)	9	-2.0 (-7.0, 3.0)
	≥18.5 kg/m^2	55	-3.0 (-24.0, 2.0)	54	-2.0 (-13.0, 2.0)
Initial symptoms	Bulbar-onset	19	-2.0 (-17.0, 1.0)	19	-2.0 (-13.0, 2.0)
	Limb-onset	44	-3.5 (-24.0, 2.0)	44	-2.0 (-12.0, 3.0)
	Upper limb-onset	31	-4.0 (-24.0, 2.0)	31	-2.0 (-12.0, 3.0)
	Lower limb-onset	13	-3.0 (-19.0, 1.0)	13	-2.0 (-7.0, 0.0)
Time from ALS symptom onset to start of run-in period	≤9 months	31	-3.0 (-19.0, 2.0)	36	-2.0 (-12.0, 0.0)
	>9 months and ≤12 months	32	-3.0 (-24.0, 0.0)	27	-2.0 (-13.0, 3.0)
%FVC at the end of run-in period	<90%	27	-5.0 (-24.0, 1.0)	28	-3.5 (-13.0, 2.0)
	≥90%	36	-2.0 (-17.0, 2.0)	35	-2.0 (-7.0, 3.0)
Prior treatment with edaravone	No	57	-3.0 (-24.0, 2.0)	59	-2.0 (-13.0, 3.0)
	Yes	6	-1.5 (-10.0, 1.0)	4	-5.0 (-9.0, -3.0)
Riluzole coadministration	No	6	-2.0 (-10.0, -1.0)	6	-3.5 (-7.0, 0.0)
	Yes	57	-3.0 (-24.0, 2.0)	57	-2.0 (-13.0, 3.0)
Age of ALS symptom onset	<65 years	36	-3.0 (-24.0, 1.0)	34	-2.0 (-12.0, 3.0)
	≥65 years	27	-3.0 (-11.0, 2.0)	29	-3.0 (-13.0, 2.0)
Diagnosis according to the updated Awaji criteria at the end of run-in period	Definite	16	-2.5 (-15.0, 2.0)	23	-2.0 (-13.0, 0.0)
	Probable and probable-laboratory supported	47	-3.0 (-24.0, 1.0)	40	-2.5 (-12.0, 3.0)
Strength of neck flexion at the end of run-in period	MRC score 5	48	-3.0 (-24.0, 2.0)	39	-2.0 (-13.0, 2.0)
	MRC score ≤4	15	-2.0 (-19.0, 1.0)	24	-4.0 (-12.0, 3.0)
ALS severity classification at the end of run-in period	Grade 1	21	-3.0 (-13.0, 1.0)	20	-2.0 (-8.0, 3.0)
	Grade 2	42	-3.0 (-24.0, 2.0)	43	-2.0 (-13.0, 2.0)
Change in ALSFRS-R total score over the run-in period	-2 points	27	-5.0 (-24.0, 2.0)	30	-3.0 (-13.0, 2.0)
	-1 point	36	-2.0 (-14.0, 1.0)	33	-2.0 (-12.0, 3.0)
ALSFRS-R total score at the end of run-in period	≤37 points	3	0.0 (-7.0, 2.0)	1	-7.0
	≥38 and ≤42 points	24	-3.5 (-19.0, 1.0)	31	-2.0 (-12.0, 3.0)
	≥43 points	36	-2.5 (-24.0, 1.0)	31	-2.0 (-13.0, 2.0)

Median (Min., Max.)

PMDA's view:

Given that Japanese Study 763 demonstrated the superiority of mecobalamin 50 mg to placebo in the primary endpoint of the change in the ALSFRS-R total score from the end of the run-in period to Week 16 of the treatment period, etc., mecobalamin demonstrated a certain clinically meaningful slowing of functional decline. As to the secondary endpoints for Japanese Study 763, the time to event during the treatment period cannot be evaluated because no events occurred in either group, but the results of other endpoints suggested a trend supporting the efficacy of mecobalamin, on the whole. There was no trend denying the efficacy of mecobalamin in a subgroup of patients with specific characteristics.

The cumulative event rate and the change in the ALSFRS-R total score through Week 182 in Japanese Study 761 were analyzed based on the point estimates. The analyses suggested a trend towards higher efficacy in the

mecobalamin group than in the placebo group. The limited placebo-controlled period of Japanese Study 763 and the decreased number of subjects analyzed with prolonged treatment preclude evaluating the long-term efficacy of mecobalamin based on the results from this study. However, taking also into account that the cumulative event rate and the ALSFRS-R total score over time following administration of mecobalamin in Japanese Study 763 tended to be consistent with the results from Japanese Study 761 concerning the cumulative event rate and the ALSFRS-R total score, the long-term efficacy of mecobalamin is also expected.

7.R.3 Safety of mecobalamin

PMDA's view:

Based on the submitted clinical study data, most of the reported adverse events were related to the primary disease or treatment of the primary disease, and there were no clear differences in the occurrence of adverse events etc. between the mecobalamin and placebo groups. When compared with the post-marketing safety profile of mecobalamin in the previously approved indications based on the periodic safety update reports for mecobalamin (October 31, 2017 to October 30, 2022) and other data, no new safety concerns about the use of mecobalamin in ALS patients have been identified.

Given the submitted clinical study data and the considerations in Sections 7.R.3.1 and 7.R.3.2, as with the use of mecobalamin in the previously approved indications, particular attention should be paid to the possible occurrence of anaphylaxis-related events following administration of mecobalamin, but other events observed in clinical studies are unlikely to become a major problem in the clinical use of mecobalamin. Mecobalamin has acceptable safety, including anaphylaxis-related events, in Japanese patients with ALS in view of its efficacy, provided that appropriate safety measures are taken.

7.R.3.1 Anaphylaxis

PMDA asked the applicant to explain the occurrence of anaphylaxis-related adverse events[26)] associated with mecobalamin.

The applicant's explanation:

As to anaphylaxis-related adverse events occurring in Japanese Studies 761, 762, and 763, circulatory collapse (1 subject) in Japanese Study 761 and circulatory collapse (2 subjects) and shock (1 subject) in Japanese Study 762 were reported. All of the 3 events of circulatory collapse were considered associated with the progression of the primary disease, and the event of shock was considered associated with postoperative haemorrhage and invasion. A causal relationship to mecobalamin was ruled out for all those events, and no other anaphylaxis-related adverse events were reported. Anaphylaxis is listed as clinically significant adverse reactions in the package insert for the currently approved injectable formulation of mecobalamin. According to the post-marketing adverse drug reaction reports submitted from the product launch (the currently approved

26) Anaphylaxis-related adverse events were defined as anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, anaphylactoid shock, circulatory collapse, Kounis syndrome, procedural shock, shock, shock symptom, type I hypersensitivity, and distributive shock in the MedDRA SMQs "anaphylactic reaction (narrow)" and "anaphylactic/anaphylactoid shock conditions (narrow)."

formulations of mecobalamin)[27] until the end of March 2024, 44 anaphylaxis- or shock-related events were reported (33 events with the injection, 11 events with the oral formulations), including 36 serious events. Among the 44 events, 1 event had a fatal outcome, 42 events had an outcome of resolving or resolved, and 1 event had an unknown outcome. The 1 death (a man in his 40s, anaphylactic shock) was reported with the injection in the fiscal year of 1996 in Japan. The patient died on his way home after receiving treatment at the medical institution. No information on the clinical course or the cause of death was available, and it was difficult to assess the causal relationship between death and mecobalamin injection.

As described above, although no anaphylaxis-related adverse events considered related to mecobalamin were reported in ALS clinical studies of mecobalamin, given that anaphylaxis- or shock-related events have been reported with the currently approved formulations of mecobalamin, anaphylaxis may occur following administration of the proposed product. Thus, as with the currently approved injectable formulation of mecobalamin, the package insert etc. will include a precautionary statement about anaphylaxis.

PMDA's view:
Although no anaphylaxis-related adverse events considered related to mecobalamin were reported in clinical studies of mecobalamin, given that anaphylaxis- or shock-related events have been reported with the currently approved formulations of mecobalamin, anaphylaxis may occur also following administration of the proposed product. As with the currently approved injectable formulation of mecobalamin, the package insert etc. for the proposed product should include a precautionary statement about anaphylaxis.

7.R.3.2 Long-term safety of mecobalamin

PMDA asked the applicant to explain the long-term safety of mecobalamin.

The applicant's explanation based on the results from Japanese Studies 761, 762, and 763, the pooled data from Japanese Studies 761 and 762 (the pooled data from Japanese Studies 761/762), etc.:
The results from Japanese Studies 763 and 761[28] showed no clear differences in the incidence of adverse events etc. between the mecobalamin and placebo groups [see Section 7], and mecobalamin had acceptable safety. When adverse events in Japanese Studies 761, 762, and 763 and pooled Japanese Studies 761/762 were counted by time to first onset, in any of the studies or the pooled studies, the frequency of first occurrence of any adverse event did not clearly increase with prolonged treatment, and there were no clear differences in the time to the first onset of adverse events among the treatment groups (Table 29 and Table 30). Moreover, the updated safety information after the data cutoff date for the latest Japanese Study 763 indicates that no events of particular concern have been accrued to date, and no clear differences have been observed compared to the previous safety information.

27) Methycobal Tablets 500 μg, September 1, 1981; Methycobal Injection 500 μg and Methycobal Tablets 250 μg, June 2, 1984; Methycobal Fine Granules 0.1%, July 2, 1984
28) Duration of study drug exposure (days [mean ± SD] and patient-years) in Japanese Study 763 (Entire period [[redacted] 20[redacted] data cutoff]), 634.5 ± 420.7 days and 187.5 patient-years; Duration of study drug exposure (days [mean ± SD] and patient-years) in Japanese Study 761, 689.0 ± 412.8 days and 234.2 patient-years in the placebo group, 704.5 ± 448.0 days and 241.8 patient-years in the mecobalamin 25 mg group, and 695.5 ± 422.3 days and 236.6 patient-years in the mecobalamin 50 mg group

Table 29. Adverse events by time to first onset based on pooled data from Japanese Studies 761/762

Treatment group of Japanese Study 761	Entire period Number of subjects with event	≤3[a)]	3-6[b)]	6-9	9-12	12-15	15-18	18-21	21-24	24-27	27-30	30-33	33-36	36-39	39-42	42-45	45-48	48-51	51-54	>54[c)]
Number of subjects																				
Placebo	44	44	42	37	32	29	26	23	22	19	17	16	13	12	12	9	8	8	7	7
Mecobalamin 25 mg	124	124	122	111	104	93	85	77	72	67	60	57	53	52	49	46	41	38	35	30
Mecobalamin 50 mg	123	123	118	113	102	95	88	80	71	67	57	51	46	45	45	45	41	40	37	32
All adverse events																				
Placebo	42 (95.5)	37 (84.1)	4 (9.5)	1 (2.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Mecobalamin 25 mg	122 (98.4)	104 (83.9)	13 (10.7)	4 (3.6)	1 (1.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Mecobalamin 50 mg	121 (98.4)	88 (71.5)	18 (15.3)	10 (8.8)	2 (2.0)	2 (2.1)	0 (0)	0 (0)	1 (1.4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

n (%)

a) ≤3 months, b) >3 months and ≤6 months, the same rule [exclusive start and inclusive end] applies hereinafter, c) >54 months

Table 30. Adverse events by time to first onset in Japanese Study 763

	Entire period	Double-blind period	≤12[a)]	12-24[b)]	24-36	36-48	48-60	60-72	72-84	84-96	96-108	108-120	120-132	132-144	144-156
Number of subjects															
All subjects	129	129	124	116	97	80	70	58	53	50	44	37	34	25	20
Placebo	64	64	61	58	45	39	31	26	25	23	18	14	14	9	7
Mecobalamin 50 mg	65	65	63	58	52	41	39	32	28	27	26	23	20	16	13
All adverse events															
All subjects	120 (93.0)	82 (63.6)	63 (50.8)	49 (42.2)	44 (45.4)	39 (48.8)	33 (47.1)	22 (37.9)	20 (37.7)	19 (38.0)	12 (27.3)	10 (27.0)	11 (32.4)	6 (24.0)	6 (30.0)
Placebo	61 (95.3)	42 (65.6)	35 (57.4)	25 (43.1)	18 (40.0)	15 (38.5)	15 (48.4)	14 (53.8)	9 (36.0)	12 (52.2)	7 (38.9)	2 (14.3)	3 (21.4)	4 (44.4)	1 (14.3)
Mecobalamin 50 mg	59 (90.8)	40 (61.5)	28 (44.4)	24 (41.4)	26 (50.0)	24 (58.5)	18 (46.2)	8 (25.0)	11 (39.3)	7 (25.9)	5 (19.2)	8 (34.8)	8 (40.0)	2 (12.5)	5 (38.5)

n (%)

a) ≤12 weeks in the extension period, b) >12 weeks and ≤24 weeks in the extension period, the same rule [exclusive start and inclusive end] applies hereinafter

PMDA's view:

Given the analyses of the data from Japanese Studies 761, 762, and 763, there are no particular concerns about the long-term treatment with mecobalamin in ALS patients at present. Moreover, the updated safety information after the data cutoff date for Japanese Study 763 indicates that no events of particular concern have been accrued to date, and there are no clear differences between the updated and previous safety information. Thus, the long-term safety of mecobalamin is acceptable.

7.R.4 Indication

PMDA asked the applicant to explain the appropriateness of the proposed indication and the proposed statement in the PRECAUTIONS CONCERNING INDICATION section, especially by referring to patients considered eligible for mecobalamin therapy in clinical practice.

The applicant's explanation:

Mecobalamin can be recommended also for ALS patients who did not meet the eligibility criteria and were not enrolled in Japanese Study 763 as described below.

- Patients with a disease duration from symptom onset of >12 months: In a subgroup of patients with a disease duration from symptom onset of >12 months in Japanese Study 761 (75 patients in the placebo group, 70 patients in the mecobalamin 25 mg group, 81 patients in the mecobalamin 50 mg group), the times from enrollment in the treatment phase to event (median [25th percentile, 75th percentile]) were 1217 days (538 days, not calculable) in the placebo group, 1250 days (576 days, not calculable) in the mecobalamin 25 mg group, and 829 days (533 days, not calculable) in the mecobalamin 50 mg group, and the changes in the ALSFRS-R total score from the end of the run-in period to the last time point (mean ± SD) were −19.9 ± 10.6 in the placebo group, −17.9 ± 11.5 in the mecobalamin 25 mg group, and −19.6 ± 10.5 in the mecobalamin 50 mg group. Neither the time to event nor the change in the ALSFRS-R total score suggested a clear efficacy of mecobalamin vs. placebo. On the other hand, as to the progression of functional impairment in ALS patients, most clinicians viewed a 50% change in the decline of the ALSFRS-R total score as "very clinically meaningful" (*Amyotroph Lateral Scler.* 2010; 11: 178-80). Given this report, the change in the ALSFRS-R total score in the placebo group in the subgroup of patients with a disease duration from symptom onset of >12 months in Japanese Study 761 was considered to represent an average rate of progression of functional impairment in ALS patients with a disease duration from symptom onset of >12 months, and "50% responders" were defined as subjects with a ≥50% reduction in the decline of the ALSFRS-R total score as compared to the time-matched mean change in the ALSFRS-R total score in the placebo group. Table 31 shows the 50% responder rate in the subgroup of patients with a disease duration from symptom onset of >12 months in Japanese Study 761. The 50% responder rate tended to be higher in the mecobalamin 50 mg group than in the placebo group at all time points.

  Regarding safety, the incidence of adverse events or adverse drug reactions in the subgroup of patients with a disease duration from symptom onset of ≤12 months was 97.9% (47 of 48 subjects) or 2.1% (1 of 48 subjects), respectively, in the placebo group, 96.3% (52 of 54 subjects) or 3.7% (2 of 54 subjects), respectively, in the mecobalamin 25 mg group, and 97.6% (41 of 42 subjects) or 4.8% (2 of 42 subjects), respectively, in the mecobalamin 50 mg group. The incidence of adverse events or adverse drug reactions in the subgroup of patients with a disease duration from symptom onset of >12 months was 100% (75 of 75 subjects) or 5.3% (4 of 75 subjects), respectively, in the placebo group, 98.6% (69 of 70 subjects) or 10.0% (7 of 70 subjects), respectively, in the mecobalamin 25 mg group, and 98.8% (80 of 81 subjects) or 6.2% (5 of 81 subjects), respectively, in the mecobalamin 50 mg group. There were no clear differences in the incidence of adverse events or adverse drug reactions according to the time from ALS symptom onset. Based on the above, although the efficacy of mecobalamin may be lower in patients with a disease duration from symptom onset of >12 months than in patients with a disease duration from symptom onset of <12 months, mecobalamin can be expected to have a certain level of efficacy, with acceptable safety.

Table 31. 50% responder rates at different time points in the subgroup of patients who entered the study >12 months after symptom onset in Japanese Study 761 (FAS)

Time point	Mean change[a)]	50% responder[b)] rate[c)]		
		Placebo	Mecobalamin 25 mg	Mecobalamin 50 mg
Week 52	-9.0	33.9% (20/59)	27.5% (14/51)	36.1% (22/61)
Week 100	-14.8	18.6% (8/43)	30.3% (10/33)	27.3% (12/44)
Week 160	-17.4	16.0% (4/25)	36.0% (9/25)	38.1% (8/21)
Week 182	-16.3	18.2% (4/22)	36.4% (8/22)	35.0% (7/20)

a) Mean change in the ALSFRS-R total score from the end of run-in period in the placebo group
b) Subjects with a ≥50% reduction in the decline of the ALSFRS-R total score as compared to the time-matched mean change in the ALSFRS-R total score from the end of run-in period in the placebo group
c) Proportion of 50% responders (Number of 50% responders/Number of subjects analyzed)

- Patients with grade ≥3 of the ALS severity classification: Since mecobalamin is expected to slow the degeneration/loss of motor neurons through its neuroprotective effect, patients with grade ≥3 of the ALS severity classification in whom a large number of motor neurons are considered to have been degenerated/lost were excluded from Japanese Studies 761 and 763. In Japanese Study 762, the changes in the ALSFRS-R total score (median [min., max.]) by ALS severity classification at baseline were −2.0 (−17, 0) in subjects with grade 1 or 2 (21 of 144 subjects) and −1 (−17, 3) in subjects with grade 3 to 5 (123 of 144 subjects). Although comparison has limitations due to the limited number of subjects, there was no trend towards major differences in the efficacy of mecobalamin according to the severity of the disease at baseline. With respect to the incidences of adverse events and adverse drug reactions by ALS severity classification at baseline in Japanese Study 762, there was no trend towards clear differences according to ALS severity, and no safety concerns about mecobalamin in subjects with grade ≥3 of the severity classification were suggested. In addition, according to clinical research in which ALS patients without respiratory failure, regardless of ALS severity classification, were treated with twice weekly mecobalamin 50 mg, the mean survival time or the period to become respirator-bound was significantly longer in the treated group than in the untreated group (*Brain Nerve.* 2007; 59: 1141-7). Based on the above, although the efficacy of mecobalamin may be lower in patients with grade ≥3 of the severity classification in whom a large number of motor neurons have been degenerated/lost than in patients with mild ALS, as motor neuron impairment continues even in patients with grade ≥3 of the severity classification, a certain level of efficacy of mecobalamin in slowing the progression of functional impairment is expected also in patients with grade ≥3 of the severity classification, and mecobalamin should have acceptable safety.
- Patients with slow or rapid disease progression (other than patients with a 1-point to 2-point decline in the ALSFRS-R total score over 12 weeks): Table 32 shows the changes in the ALSFRS-R total score from the end of the run-in period to the last time point in subjects with a 1-point, 2-point, or 3-point decline in the ALSFRS-R total score over the run-in period in Japanese Study 761. A trend towards greater improvement in the point estimate in the mecobalamin group than in the placebo group was suggested also in subjects with a 3-point decline in the ALSFRS-R total score, as in subjects with a 1-point to 2-point decline. Given this finding, a certain level of efficacy of mecobalamin is expected also in patients with rapid disease progression. The results from Japanese Study 761 have demonstrated the safety of mecobalamin in these patients.

Table 32. Subgroup analysis according to the change in the ALSFRS-R total score over the run-in period in Japanese Study 761 (FAS)

		Placebo		Mecobalamin 25 mg		Mecobalamin 50 mg	
		N	Median	N	Median	N	Median
Change in ALSFRS-R total score over the run-in period	-1 point	42	-20.5 (-38, 1)	45	-19.0 (-42, 2)	42	-19.5 (-38, 1)
	-2 points	46	-22.0 (-42, -2)	41	-22.0 (-39, 0)	45	-19.0 (-39, -1)
	-3 points	35	-27.0 (-40, -1)	38	-24.0 (-39, -6)	35	-22.0 (-39, -2)

Median (Min., Max.)

On the other hand, substantial clinical heterogeneity among patients with ALS is seen, and some of ALS patients with slow disease progression gradually develop functional impairment over ≥10 years from symptom onset. In such patients progressing slowly, the changes in the ALSFRS-R score during a short clinical study are minimal, and it is very difficult to detect significant efficacy of a drug in the clinical study. However, there is no scientific evidence supporting differences in the clinical symptoms or pathology of ALS between these patients with slow disease progression and patients with rapid disease progression. The efficacy and safety of mecobalamin in patients with slow disease progression should not substantially be different from those in ALS patients with a 1-point to 2-point decline in the ALSFRS-R total score over the run-in period. A certain level of efficacy of mecobalamin is expected also in patients with slow disease progression, and mecobalamin should have acceptable safety.

- Patients with ambulatory difficulties due to their physical status: Although ambulatory patients with ALS were included in Japanese Study 763, if ambulatory visits became difficult due to disease progression etc., study drug administration at the patient's home or nearby medical institution was permitted. Among patients enrolled in the extension phase of Japanese Study 763, 57 of 124 subjects (46%) self-administered at least 1 dose of study drug, and >50% of subjects are considered to have received study drug outside the study site. Since the efficacy and safety results during the treatment and extension periods of Japanese Study 763 include also the results from patients with ambulatory difficulties due to their physical status, etc., the efficacy and safety of mecobalamin are expected also in patients with ambulatory difficulties due to their physical status.
- Patients with %FVC ≤60%: %FVC (mean ± SD) before the start of Japanese Study 762 was 58.76 ± 30.93 (73 subjects). The change in the ALSFRS-R total score from baseline (of Study 762) to the last assessment (Week 52) (median [min., max.]) in a subgroup of patients with %FVC ≤60% (42 subjects) was −1.0 (−17, 0). There were no major differences as compared to the change in the ALSFRS-R total score from baseline to the last assessment (Week 52) in the overall population (143 subjects) (median [min., max.], −1.0 [−17, 3]). According to safety analyses of the data through the last assessment (Week 52) from Japanese Study 762, the incidence of adverse events or adverse drug reactions in the subgroup of patients with %FVC ≤60% was 88.1% (37 of 42 subjects) or 4.8% (2 of 42 subjects), respectively. There were no clear differences as compared to the incidence of adverse events or adverse drug reactions in the overall population (94.4% [136 of 144 subjects] or 3.5% [5 of 144 subjects], respectively). Adverse events reported in subjects with %FVC ≤60% included conjunctivitis, diarrhoea, constipation, pyrexia, stomatitis, and hepatic function abnormal, but no serious adverse drug reactions or adverse drug reactions leading to treatment discontinuation, etc., were reported. There were no adverse events or safety concerns unique to subjects with %FVC ≤60%. Based on the above, the efficacy and safety of mecobalamin are expected also in ALS patients with %FVC ≤60%.
- Patients with previous use of non-invasive ventilation or undergoing tracheostomy: In Japanese Study 762, 87 of 144 subjects had previously used non-invasive ventilation or were undergoing tracheostomy at

baseline. The change in the ALSFRS-R total score from baseline to the last assessment (Week 52) (median [min., max.]) in this subgroup was −2.0 (−12, 3), and there were no clear differences as compared to the change in the ALSFRS-R total score from baseline to the last assessment (Week 52) in the overall population (143 subjects) (median [min., max.], −1.0 [−17, 3]). According to the safety analyses of the data through the last assessment (Week 52) from Japanese Study 762, the incidence of adverse events or adverse drug reactions in this subgroup was 95.4% (83 of 87 subjects) or 3.4% (3 of 87 subjects), respectively, and there were no major differences as compared to the incidence of adverse events or adverse drug reactions in the overall population (94.4% [136 of 144 subjects] or 3.5% [5 of 144 subjects], respectively). Adverse events reported in this subgroup included pneumonia, nasopharyngitis, bronchitis, diarrhoea, constipation, pyrexia, erythema, excessive granulation tissue, and eczema, but there were no serious adverse drug reactions or adverse drug reactions leading to treatment discontinuation. No events of safety concern were reported in the clinical use of mecobalamin in this subgroup. Based on the above, the efficacy and safety of mecobalamin are expected also in patients with previous use of non-invasive ventilation or undergoing tracheostomy before initiation of treatment with mecobalamin.

- Patients receiving concomitant edaravone: The concomitant use of edaravone with mecobalamin was prohibited during the treatment period of Japanese Study 763, but permitted during the extension period of Japanese Study 763. During the extension period of Japanese Study 763, 23 subjects receiving placebo during the treatment period and 32 subjects receiving mecobalamin 50 mg during the treatment period received concomitant edaravone. Table 33 shows summary statistics of the ALSFRS-R total score and the change by concomitant use of edaravone. Since the timing and duration of edaravone administration differed from subject to subject, and the number of subjects was also limited, rigorous comparison is difficult. However, there was no trend towards major differences in the ALSFRS-R total score over time according to concomitant use of edaravone.

Table 33. Subgroup analyses of ALSFRS-R total score during the extension period of Japanese Study 763 according to concomitant use of edaravone (FAS)

	With edaravone				Without edaravone			
	Placebo/Mecobalamin 50 mg		Mecobalamin 50 mg /Mecobalamin 50 mg		Placebo/Mecobalamin 50 mg		Mecobalamin 50 mg /Mecobalamin 50 mg	
	Total score	Change	Total score	Change	Total score	Change	Total score	Change
Week 12	36.0 (15.0, 46.0)	-7.5 (-27.0, 1.0)	36.5 (26.0, 47.0)	-4.0 (-18.0, 2.0)	36.0 (16.0, 44.0)	-5.0 (-25.0, 0.0)	38.0 (22.0, 46.0)	-6.0 (-19.0, 2.0)
Week 24	31.0 (13.0, 46.0)	-11.0 (-30.0, 1.0)	35.0 (16.0, 47.0)	-7.0 (-25.0, 2.0)	34.0 (17.0, 43.0)	-7.0 (-24.0, -1.0)	37.0 (19.0, 46.0)	-7.0 (-22.0, 0.0)
Week 48	33.0 (13.0, 43.0)	-10.0 (-33.0, -2.0)	35.0 (14.0, 45.0)	-8.5 (-24.0, 0.0)	30.0 (16.0, 42.0)	-11.0 (-28.0, -2.0)	36.0 (14.0, 46.0)	-9.0 (-30.0. 0.0)

Median (Min., Max.)

Regarding the safety of mecobalamin with or without edaravone during the extension period of Japanese Study 763, the incidence of adverse events or adverse drug reactions among subjects with concomitant use of edaravone was 91.3% (21 of 23 subjects) or 0% (0 of 23 subjects), respectively, in subjects receiving placebo during the treatment period and 87.5% (28 of 32 subjects) or 3.1% (1 of 32 subjects), respectively, in subjects receiving mecobalamin 50 mg during the treatment period. The incidence of adverse events or adverse drug reactions among subjects without concomitant use of edaravone was 89.5% (34 of 38 subjects) or 5.3% (2 of

38 subjects), respectively, in subjects receiving placebo during the treatment period and 83.9% (26 of 31 subjects) or 9.7% (3 of 31 subjects), respectively, in subjects receiving mecobalamin 50 mg during the treatment period. There were no major differences in the safety profile of mecobalamin, including the incidence of main adverse events, according to concomitant use of edaravone.

PMDA's view:
Patients with a disease duration of >12 months, grade ≥3 of the ALS severity classification, slow disease progression, or rapid disease progression, etc. were not enrolled in Japanese Study 763. Information on the efficacy and safety of mecobalamin in these patients is limited, but can be inferred, to a certain extent, from the results from Japanese Studies 761 and 762 etc., and the efficacy of mecobalamin may be expected also in some patients in these populations. The safety profile of the proposed product is similar to those of the currently approved formulations of mecobalamin. ALS has a very poor prognosis, and current treatment options are very limited. Taking also account of these points, there is little need to uniformly restrict the use of mecobalamin in the patient populations that were not evaluated in Japanese Study 763, from a medical point of view, i.e., providing an opportunity to offer a treatment option that can slow the progression of functional impairment in ALS, also to these patients. Thus, the proposed indication of "Slowing of the progression of functional impairment in patients with amyotrophic lateral sclerosis (ALS)" is acceptable. However, prior to the use of mecobalamin, it is important that physicians decide whether to use mecobalamin, with an understanding of the clinical study results including the characteristics of patients enrolled in clinical studies, e.g., disease duration, ALS severity, and respiratory function. Thus, the package insert etc. should advise that eligible patients must be selected appropriately by physicians with a full understanding of the study populations and results of clinical studies and clinical study results including patient characteristics.

7.R.5 Clinical positioning

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

The applicant's explanation:
Currently in Japan, riluzole and edaravone have been approved as ALS treatments. As symptomatic therapies, opioids are used to relieve dyspnoea or pain, and anti-spasticity agents etc. are used to treat spasticity in ALS (Practical Guideline for Amyotrophic Lateral Sclerosis 2023, Drafting Committee for Practical Guideline for Amyotrophic Lateral Sclerosis ed.). However, as these treatments have limited effects and are inadequate to slow the progression of the disease at present, a new treatment option is required.

Japanese Study 763 demonstrated the superiority of mecobalamin to placebo in the primary endpoint of the change in the ALSFRS-R total score from the end of the run-in period to Week 16 of the treatment period [see Section 7.R.2] and its acceptable safety [see Section 7.R.3]. Patients with a disease duration of >12 months or grade ≥3 of the ALS severity classification, etc., were excluded from Japanese Study 763, and the efficacy of mecobalamin in these ALS patients was not evaluated. However, as described in Section 7.R.4, the efficacy of mecobalamin is expected also in these patients.

Based on the above, mecobalamin will become a new treatment option for slowing the progression of functional impairment in ALS patients.

PMDA's view:
Given the submitted clinical study results and the treatment paradigm for ALS, mecobalamin can become a new treatment option for slowing the progression of functional impairment in ALS patients. Taking account of the study population of a confirmatory study of mecobalamin, i.e., Japanese Study 763, the study results, etc., prior to the use of mecobalamin in ALS patients, it is important that physicians carefully balance the expected benefits and risks for individual patients, with an understanding of the clinical study results including the characteristics of patients included in clinical studies, and carefully decide whether to use mecobalamin, referring also to the latest information, e.g., the clinical practice guidelines for ALS. The positioning of mecobalamin in the treatment algorithm for ALS is expected to be discussed at the relevant academic societies etc., taking also account of any new information obtained after marketing, etc.

7.R.6 Dosage and administration

PMDA asked the applicant to explain the appropriateness of the dosing regimen of mecobalamin, taking also account of the actual intervals between doses in clinical studies.

The applicant's explanation:
As described in Sections 7.R.2 and 7.R.3, Japanese Study 763 demonstrated the superiority of mecobalamin 50 mg administered intramuscularly twice weekly to placebo and its acceptable safety.

In Japanese Studies 761, 762, and 763, study drug was administered twice weekly, and the interval between doses had to be at least 1 day. The distribution of the intervals between doses of mecobalamin within 1 week (modal value) was similar among the studies, and the intervals between doses were 3 days (45.0%-48.1%), 2 days (27.3%-36.4%), 4 days (17.8%-23.2%), and 5 days (0.8%-1.4%) (in descending order of frequency). Although many subjects received the doses of mecobalamin at intervals of 3 to 4 days within 1 week, some subjects received doses at intervals of 2 or 5 days. Based on the results from Foreign Study 002, the accumulation ratio after once-daily intramuscular administration of mecobalamin 50 mg for 7 days was approximately 1, and there was no accumulation of mecobalamin with once daily dosing [see Section 6.2.2.2]. Mecobalamin was rapidly eliminated, and plasma mecobalamin concentrations at 24 hours after dosing were below the LLOQ. Thus, the variability in the interval between doses within 1 week is not expected to have a major impact on mecobalamin exposure, and there are no precautions regarding the interval between doses of mecobalamin within 1 week, from the clinical pharmacology standpoint.

Based on the above, the dosing regimen of mecobalamin 50 mg administered intramuscularly twice weekly was selected. Given clinical experience with mecobalamin administered at different intervals within 1 week in

the clinical studies and from the clinical pharmacology standpoint, there is no need to specify the interval between doses within 1 week in the DOSAGE AND ADMINISTRATION section of the package insert.

PMDA's view:
As described in Sections 7.R.2 and 7.R.3, the efficacy of mecobalamin 50 mg administered intramuscularly twice weekly in ALS patients was demonstrated, and mecobalamin had acceptable safety.

In Japanese Studies 761, 762, and 763, mecobalamin was to be administered twice weekly, and the interval between doses was to be at least 1 day. Some patients received doses of mecobalamin at intervals of 2 to 5 days within 1 week. Given that there was no accumulation after once-daily intramuscular administration of mecobalamin 50 mg [see Section 6.2.2.2], and that the interval between doses within 1 week is not expected to have a major impact on mecobalamin exposure, there is no need to specify the interval between doses within 1 week in the DOSAGE AND ADMINISTRATION section of the package insert.

Based on the above, the proposed dosing regimen of mecobalamin 50 mg administered intramuscularly twice weekly in ALS patients is acceptable.

7.R.7 Self-administration

The applicant's explanation about the efficacy and safety of self-administered mecobalamin:
During the extension period of Japanese Study 763, study drug was self-administered by subjects or their family members who had been educated and trained to self-administer study drug and were considered capable to self-administer study drug. Among 125 subjects who entered the extension phase, 1 ineligible subject was excluded. Of the 124 subjects, 57 (46.0%) self-administered at least 1 dose of study drug. The duration of self-administration in those self-administering study drug (mean ± SD) was 86.97 ± 56.64 weeks, and the maximum duration of self-administration was 214 weeks. The mean proportion of duration of self-administration during the extension period was 84.0%.

Table 34 shows the ALSFRS-R total score by self-administration status during the extension period of Japanese Study 763. Although rigorous evaluation is difficult due to the results of the limited subgroups, there were no clear differences in the ALSFRS-R total score over time throughout the evaluation period according to self-administration status.

Table 34. Subgroup analysis of ALSFRS-R total score in Japanese Study 763 according to self-administration status (FAS)

	Self-administration			Non-self-administration		
Time point	N	Mean	Median	N	Mean	Median
End of run-in period	57	42.3 ± 2.9	43.0 (31.0, 47.0)	67	42.2 ± 2.4	42.0 (35.0, 46.0)
Week 28	57	35.9 ± 7.4	37.0 (15.0, 47.0)	63	35.3 ± 6.8	36.0 (18.0, 46.0)
Week 40	53	33.0 ± 9.0	36.0 (13.0, 47.0)	49	33.4 ± 7.6	35.0 (13.0, 46.0)
Week 52	44	32.5 ± 9.0	34.0 (15.0, 47.0)	38	31.9 ± 8.2	33.0 (13.0, 46.0)
Week 64	39	30.8 ± 9.8	35.0 (14.0, 45.0)	34	30.5 ± 8.9	30.5 (13.0, 46.0)
Week 76	34	30.5 ± 10.7	35.0 (8.0, 45.0)	25	30.2 ± 8.8	31.0 (16.0, 46.0)
Week 88	32	29.1 ± 11.5	32.5 (8.0, 45.0)	24	27.8 ± 9.7	28.0 (12.0, 46.0)
Week 100	29	29.1 ± 11.3	31.0 (5.0, 45.0)	20	28.0 ± 8.9	26.0 (14.0, 46.0)
Week 112	26	27.8 ± 11.3	29.0 (6.0, 44.0)	17	27.2 ± 9.6	30.0 (13.0, 46.0)
Week 124	25	28.3 ± 10.8	28.0 (2.0, 44.0)	15	26.6 ± 9.6	24.0 (12.0, 46.0)
Week 136	20	30.3 ± 9.1	33.0 (12.0, 44.0)	14	25.2 ± 11.0	22.0 (8.0, 46.0)
Week 148	17	27.4 ± 9.7	30.0 (12.0, 40.0)	10	25.1 ± 11.8	21.5 (11.0, 46.0)
Week 160	14	26.0 ± 10.0	28.0 (12.0, 40.0)	7	21.9 ± 11.7	18.0 (10.0, 38.0)
Week 172	11	24.9 ± 10.1	23.0 (12.0, 40.0)	6	21.7 ± 12.0	23.0 (5.0, 36.0)
Week 184	9	23.7 ± 10.5	20.0 (12.0, 40.0)	5	23.0 ± 14.1	26.0 (2.0, 40.0)
Week 196	6	22.0 ± 11.4	17.0 (12.0, 40.0)	5	23.0 ± 14.0	26.0 (2.0, 39.0)
Week 208	3	12.3 ± 1.5	12.0 (11.0, 14.0)	4	22.0 ± 15.7	24.0 (2.0, 38.0)
Week 220	1	14.0	14.0	1	18.0	18.0

Mean ± SD, Median (Min., Max.)
Extension period (from Week 16 onward)

Table 35 shows the incidence of adverse events occurring after the initiation of treatment with mecobalamin by self-administration status during the extension period of Japanese Study 763. Adverse events reported at a ≥5% higher incidence in subjects self-administering mecobalamin than in subjects not self-administering mecobalamin were wound complication (14.0% [8 of 57 subjects] in subjects self-administering mecobalamin, 3.0% [2 of 67 subjects] in subjects not self-administering mecobalamin, the same order applies hereinafter), cataract (5.3% [3 of 57 subjects], 0% [0 of 67 subjects]), and rash (8.8% [5 of 57 subjects], 1.5% [1 of 67 subjects]). A causal relationship to study drug was ruled out for all of the events of wound complication, rash, and cataract. The events of wound complication were gastrostomy- or central venous port placement-related events or complications after tracheal dilation surgery etc. due to disease progression, all of which are considered unrelated to self-administration of mecobalamin. The incidences of adverse events for which a causal relationship to study drug could not be ruled out were 3.5% (2 of 57 subjects [Wolff-Parkinson-White syndrome; and headache (1 subject each)]) in subjects self-administering mecobalamin and 3.0% (2 of 67 subjects [dermatitis acneiform; and local reaction and injection site reaction]) in subjects not self-administering mecobalamin. The incidences of serious adverse events occurring after the initiation of treatment with mecobalamin during the extension period were 29.8% (17 of 57 subjects) in subjects self-administering mecobalamin and 52.2% (35 of 67 subjects) in subjects not self-administering mecobalamin, and serious adverse events reported by ≥2 subjects self-administering mecobalamin were respiratory failure (5 subjects) and pneumonia aspiration (3 subjects), but a causal relationship to study drug was ruled out for all those events.

Table 35. Incidence of all adverse events by self-administration status and adverse events reported by ≥5% of subjects in either group (safety analysis set)

	Self-administration (N = 57)	Non-self-administration (N = 67)
Any adverse event	47 (82.5)	60 (89.6)
Adverse events reported by ≥5% of subjects in either group		
Constipation	12 (21.1)	18 (26.9)
Contusion	9 (15.8)	9 (13.4)
Wound complication	8 (14.0)	2 (3.0)
Nasopharyngitis	7 (12.3)	11 (16.4)
Fall	6 (10.5)	7 (10.4)
Insomnia	5 (8.8)	11 (16.4)
Pruritus	5 (8.8)	9 (13.4)
Respiratory failure	5 (8.8)	7 (10.4)
Rash	5 (8.8)	1 (1.5)
Stomatitis	4 (7.0)	6 (9.0)
Bronchitis	4 (7.0)	3 (4.5)
Eczema	4 (7.0)	3 (4.5)
Back pain	3 (5.3)	9 (13.4)
Pneumonia aspiration	3 (5.3)	8 (11.9)
Dizziness	3 (5.3)	6 (9.0)
Diarrhoea	3 (5.3)	4 (6.0)
Decubitus ulcer	3 (5.3)	3 (4.5)
Musculoskeletal pain	3 (5.3)	2 (3.0)
Depression	3 (5.3)	1 (1.5)
Cough	3 (5.3)	1 (1.5)
Dermatitis contact	3 (5.3)	1 (1.5)
Cataract	3 (5.3)	0
Haemorrhoids	1 (1.8)	4 (6.0)
Pneumonia	0	8 (11.9)

n (%)

Based on the above, the clinical study showed no particular problems with the efficacy and safety of mecobalamin when self-administered by ALS patients or their family members. The precautionary statements in the package insert will include the following: Mecobalamin should be self-administered by patients or their family members under the supervision and guidance of physicians after the patients or their family members are fully educated and trained to ensure that they are capable to self-administer mecobalamin appropriately.

PMDA's conclusion:

Given the applicant's explanation, there were no particular problems with self-administration of mecobalamin by patients or their family members who had been educated and trained to self-administer mecobalamin and were considered to have acquired self-administration skills appropriately, under the supervision and guidance of physicians.

7.R.8 Post-marketing investigations

The applicant's explanation about post-marketing investigations of mecobalamin:

As discussed in Section 7.R.3, as with use in the previously approved indications, attention should be paid to the possible occurrence of anaphylaxis-related events, but no other events of particular concern following the routine and long-term administration of mecobalamin, have been reported to date, and no new concerns exceeding the safety risk of mecobalamin in the previously approved indications have been suggested. In addition, mecobalamin has been used for the previously approved indications for a long time, and its safety profile has been established. Given these points, the safety of mecobalamin including its long-term safety in Japanese patients with ALS is manageable by collecting data through routine pharmacovigilance practices.

PMDA’s view:

As discussed in Section 7.R.3, as with use in the previously approved indications, attention should be paid to the possible occurrence of anaphylaxis-related events. However, the currently available study results and other data have shown no events of particular concern following administration of mecobalamin including its long-term use and have suggested no new concerns exceeding the safety risk of mecobalamin in the previously approved indications. Although the patient populations evaluated in clinical studies and the number of Japanese patients with ALS studied were limited, given that the safety profile of mecobalamin has been established based on the long-term clinical experience with mecobalamin in the previously approved indications, data on the long-term safety of mecobalamin and other data in Japanese patients with ALS should be collected through routine pharmacovigilance practices. If a safety signal is detected through these activities, the conduct of post-marketing surveillance etc. should be considered as needed.

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

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

The inspection and assessment are currently ongoing, and their results and PMDA's conclusion will be reported in the Review Report (2).

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

The inspection is currently ongoing, and its results and PMDA's conclusion will be reported in the Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that mecobalamin has efficacy in slowing the progression of functional impairment in ALS, and that mecobalamin has acceptable safety in view of its benefits. Mecobalamin is clinically meaningful because it offers a new treatment option for patients with ALS.

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

Review Report (2)

August 7, 2024

Product Submitted for Approval

Brand Name	Rozebalamin for Injection 25 mg
Non-proprietary Name	Mecobalamin
Applicant	Eisai Co., Ltd.
Date of Application	January 26, 2024

List of Abbreviations

See Appendix.

1. Content of the Review

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

At the Expert Discussion, the expert advisors supported PMDA's conclusions on the efficacy of mecobalamin and dosage and administration presented in the Review Report (1).

1.1 Indication and clinical positioning

The expert advisors made the following comment on the indication and clinical positioning of mecobalamin.

- PMDA's conclusion (Mecobalamin may be effective also in patient populations that were not evaluated in Japanese Study 763, and there is little need to uniformly restrict the use of mecobalamin as a treatment option for ALS with poor prognosis) is appropriate. However, treatment with mecobalamin should not be continued aimlessly just because mecobalamin is highly safe. The key point is that treating physicians decide whether to use mecobalamin, with an understanding of the results from Japanese Study 763. The following statement should be included in the PRECAUTIONS CONCERNING INDICATION section of the package insert: Eligible patients must be selected by physicians with a full understanding of clinical study results including the characteristics of patients enrolled in clinical studies.

In view of the discussions presented in the Review Report (1) and comments from the expert advisers at the Expert Discussion, PMDA concluded as follows:
The indication should be “slowing of the progression of functional impairment in patients with amyotrophic lateral sclerosis (ALS).” The following statement should be included in the PRECAUTIONS CONCERNING INDICATION section: Eligible patients must be selected by physicians with a full understanding of the characteristics of patients enrolled in clinical studies, e.g., disease duration, ALS severity, and respiratory function, and the study results and of the efficacy and safety of mecobalamin. The CLINICAL STUDIES section of the package insert and the materials for healthcare professionals should provide information on the patient population of Japanese Study 763 and the obtained study results.

The expert advisors supported the above conclusions. PMDA instructed the applicant to respond to the above points, and the applicant agreed to take appropriate action.

1.2 Safety, post-marketing investigations, and risk management plan (draft)

The expert advisors made the following comment on the safety of mecobalamin and post-marketing investigations and supported PMDA’s conclusions presented in Sections “7.R.3 Safety” and “7.R.8 Post-marketing investigations” in the Review Report (1).

- As with the currently approved formulations of mecobalamin, attention should be paid to the possible occurrence of anaphylaxis-related events. Although there are major differences in the dose of mecobalamin between the currently approved formulations and the proposed product, the obtained clinical study results etc. present no particular concerns about the safety of the proposed product including its long-term safety. Taking also into account that there is no accumulation after administration of the proposed product, it is appropriate, at present, to collect data on the safety etc. of mecobalamin in Japanese patients with ALS in clinical practice through routine pharmacovigilance practices, instead of conducting post-marketing surveillance etc.

In view of the discussions presented in Section “7.R.8 Post-marketing investigations” in the Review Report (1) and comments from the expert advisers at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for mecobalamin should include the safety specification presented in Table 36, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 37.

Table 36. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
● Anaphylaxis	● None	● None
Efficacy specification		
● None		

Table 37. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
● Early post-marketing phase vigilance	● Develop information materials (a proper use guide) to be distributed to healthcare professionals ● Disseminate data gathered during early post-marketing phase vigilance

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

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

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

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

The new drug application data (CTD 5.3.5.1.2) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that since the clinical study as a whole was performed in compliance with GCP, there were no obstacles to conducting its review based on the application documents submitted. The inspection revealed the following findings at some of the study sites, although the findings did not affect the overall assessment of the study significantly. These study sites were notified of these matters and asked for corrective actions.

[Findings requiring corrective actions]

Study sites

- Using the written information that did not receive approval of the institutional review board, consent to participate in the clinical study was obtained from some subjects.
- The head of the medical institution received an audit report as stipulated in Article 26-9, Paragraph 3 of the Ministerial Ordinance on Good Clinical Practice, but did not seek the opinion of the institutional review board, with respect to whether the clinical study was being conducted or had been conducted properly at the medical institution.
- Some subjects had difficulty in signing the informed consent form by themselves due to the effects of the disease. Although these subjects provided oral consent and had the informed consent form signed by their representatives, there were informed consent forms that did not contain the name of the subject.
- Using the revised written information, a new written content to continue participation in the clinical study was not obtained from some subjects.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following condition. Since the product received an orphan drug designation for the claimed indication, the re-examination period is 10 years. The product is not classified as a biological product or a specified biological product. The drug product is not classified as a poisonous drug or a powerful drug.

Indication

Slowing of the progression of functional impairment in patients with amyotrophic lateral sclerosis (ALS)

Dosage and Administration

The usual adult dosage is 50 mg of mecobalamin injected intramuscularly, once daily, twice weekly.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Appendix

List of Abbreviations

ALS	Amyotrophic lateral sclerosis
ALSAQ-40	40-item amyotrophic lateral sclerosis assessment questionnaire
ALSFRS-R	Amyotrophic lateral sclerosis functional rating scale-revised
AMED	Japan Agency for Medical Research and Development
AUC	Area under the concentration-time curve
$AUC_{0\text{-}8h}$	Area under the concentration-time curve from zero time to 8 hours
$AUC_{0\text{-}24h}$	Area under the concentration-time curve from zero time to 24 hours
$AUC_{0\text{-}t}$	Area under the concentration-time curve from zero time to time of last quantifiable concentration
$AUC_{0\text{-}inf}$	Area under the concentration-time curve from zero time extrapolated to infinite time
BCRP	Breast cancer resistance protein
BMI	body mass index
CL/F	Apparent total clearance following extravascular administration
CMAP	Compound muscle action potential
C_{max}	Maximum observed concentration
CQA	Critical quality attribute
CTD	Common Technical Document
CYP	Cytochrome P450
ES cell	Embryonic stem cell
eq.	Equivalent
FAS	Full Analysis Set
FOB	Functional observational battery
Foreign Study 002	Study E0302-E044-002 (Reference data CTD 5.3.3.1.2)
hERG	Human ether-à-go-go related gene
HEK293 cells	Human embryonic kidney 293 cells
FVC	Forced vital capacity
HPLC	High performance liquid chromatography
ICH Q3B guideline	Revision of "Revision of the Guideline on Impurities in New Drug Products" (PFSB/ELD Notification No. 0703004 dated July 3, 2006)
Japanese Study 761	Study E0302-J081-761 (CTD 5.3.5.1.1)
Japanese Study 762	Study E0302-J081-762 (CTD 5.3.5.2.1 to 5.3.5.2.4)
Japanese Study 763	Study E0302-TOK-763 (CTD 5.3.5.1.2 and 5.3.5.1.3)
JP	the Japanese Pharmacopoeia
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
NSC-34	Mouse Motor Neuron-Like Hybrid Cell Line
NSC-34D	Differentiated form of a motor NSC-34 cell line
iPS cell	Induced pluripotent stem cell
LOCF	Last observation carried forward
MATE	Multidrug and toxin extrusion
MedDRA	Medical Dictionary for Regulatory Activities
MMT	manual muscle testing
mRNA	Messenger ribonucleic acid
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
P-gp	P-glycoprotein
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
RH	Relative Humidity

SMQ	Standardized MedDRA query
SOD1	Cu/Zn superoxide dismutase
$t_{1/2}$	Terminal elimination phase half-life
Tg	Transgenic
The active substance	mecobalamin
The product	Rozebalamin for Injection 25 mg
t_{max}	Time at which the highest drug concentration occurs
UV/VIS	Ultraviolet-visible spectroscopy
Vz/F	Apparent volume of distribution at terminal phase