Report on the Deliberation Results

December 13, 2021
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Vyvgart for Intravenous Infusion 400 mg
Non-proprietary Name	Efgartigimod Alfa (Genetical Recombination) (JAN*)
Applicant	Argenx Japan K.K.
Date of Application	April 19, 2021

Results of Deliberation

In its meeting held on November 26, 2021, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is classified as a biological product, and the re-examination period is 10 years. The drug product and its drug substance are both classified as powerful drugs.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because of the limited data from Japanese clinical studies, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, until data are collected from a specified number of patients, to understand the characteristics of patients treated with the product and obtain safety and efficacy data early so as to take necessary measures for the product to be used properly.

**Japanese Accepted Name (modified INN)*

Review Report

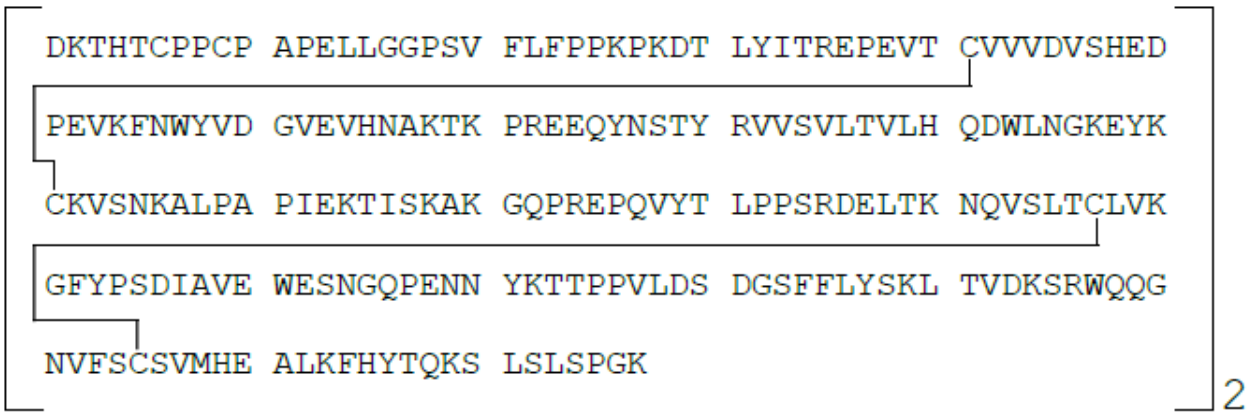
November 17, 2021
Pharmaceuticals and Medical Devices Agency

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	Vyvgart for Intravenous Infusion 400 mg
Non-proprietary Name	Efgartigimod Alfa (Genetical Recombination)
Applicant	Argenx Japan K.K.
Date of Application	April 19, 2021
Dosage Form/Strength	Injection in 20-mL vials, each containing 400 mg of Efgartigimod Alfa (Genetical Recombination).
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Definition	Efgartigimod Alfa is a recombinant human IgG1 Fc domain analog corresponding to amino acid residues at positions 221−447 (Eu numbering) of human IgG1, and the amino acid residues of Efgartigimod Alfa at positions 32, 34, 36, 213, and 214 are substituted by Tyr, Thr, Glu, Lys, and Phe, respectively. Efgartigimod Alfa is produced in Chinese hamster ovary cells. Efgartigimod Alfa is a glycoprotein (molecular weight: ca. 54,000) composed of 2 subunits consisting of 227 amino acid residues each.

Structure

Amino acid sequence and disulfide bonds



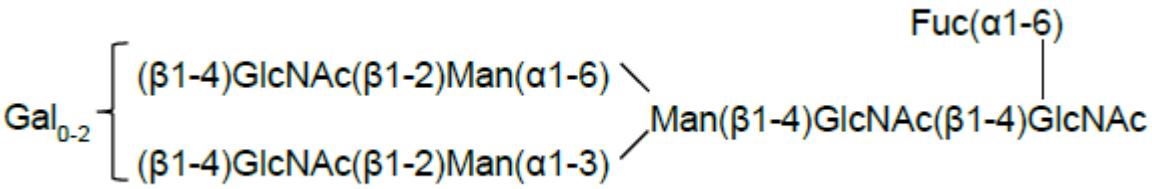
Glycosylation: N77

Processing, partial: K227

Inter-subunit disulfide bonds: solid lines

Intra-subunit disulfide bond: C6-C6, C9-C9

Deduced structure of major glycan



Molecular formula: $C_{2310}H_{3554}N_{602}O_{692}S_{14}$ (protein moiety, dimer), $C_{1155}H_{1779}N_{301}O_{346}S_7$ (monomer)

Molecular weight: 51,279.46 (protein moiety, dimer), 25,641.75 (monomer)

Items Warranting Special Mention Orphan drug (Orphan Drug Designation No. 467 of 2020 [*R2 yaku*]; PSEHB/PED Notification No. 0605-1 dated June 5, 2020, 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 the treatment of generalized myasthenia gravis (only for patients who are not adequately responsive to steroids or nonsteroidal immunosuppressants), 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 approval conditions.

Indication	Generalized myasthenia gravis (only for patients who are not adequately responsive to steroids or nonsteroidal immunosuppressants)
Dosage and Administration	The usual adult dosage is 10 mg/kg of Efgartigimod Alfa (Genetical Recombination) administered as an intravenous infusion over 1 hour for 4 times at weekly intervals. This treatment cycle is repeated.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because of the limited data from Japanese clinical studies, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, until data are collected from a specified number of patients, to understand the characteristics of patients treated with the product and obtain safety and efficacy data early so as to take necessary measures for the product to be used properly.

Attachment

Review Report (1)

October 6, 2021

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	Vyvgart for Intravenous Infusion 400 mg
Non-proprietary Name	Efgartigimod Alfa (Genetical Recombination)
Applicant	Argenx Japan K.K.
Date of Application	April 19, 2021
Dosage Form/Strength	Injection in 20-mL vials, each containing 400 mg of Efgartigimod Alfa (Genetical Recombination)
Proposed Indication	Generalized myasthenia gravis
Proposed Dosage and Administration	The usual adult dosage is 10 mg/kg (bodyweight) of Efgartigimod Alfa (Genetical Recombination) administered as an intravenous infusion over 1 hour for 4 times at weekly intervals. This cycle may be repeated depending on the patient's symptoms.

Table of Contents

List of Abbreviations

See Appendix.

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

Myasthenia gravis (MG) is an autoimmune disease characterized by generalized muscle weakness, and is a designated intractable disease in Japan. MG involves impaired signaling from neurons to muscles at the postsynaptic membrane of the neuromuscular junction due to autoantibodies directed against the acetylcholine receptor (AChR), muscle-specific kinase (MuSK), lipoprotein-related protein 4 (LRP4), etc. (*Autoimmun Rev.* 2013;12:918-23, *Lancet Neurol.* 2015;14:1023-36). MG is roughly categorized into the ocular muscle type and the generalized type according to the muscle group affected, while it primarily manifests with ocular symptoms (eyelid ptosis, double vision) frequently. Over 80% of patients experience the progression of ocular muscle MG to generalized MG within 2 years of onset (*Muscle Nerve.* 2008;37:141-9). Generalized muscle weakness impairs movement, articulation, swallowing, and vision, causing respiratory dysfunction and extreme fatigue, and 15% to 20% of patients with MG experience MG crisis that requires mechanical ventilation via endotracheal intubation (*Muscle Nerve.* 2008;37:141-9, *Neurohospitalist.* 2011;1:16-22). Efgartigimod alfa was designated as an orphan drug on June 5, 2020, with an intended indication of "generalized myasthenia gravis (gMG)" (Orphan Drug Designation No. 467 of 2020 [*R2 yaku*], PSEHB/PED Notification No. 0605-1 dated June 5, 2020 by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare).

Efgartigimod alfa is a human immunoglobulin G1 (IgG1) Fc fragment with modified amino acid residues and targets neonatal Fc receptor (FcRn). When bound to the FcRn, efgartigimod alfa blocks the binding of endogenous IgG to FcRn and inhibits the recycling of IgG, thereby accelerating the lysosomal degradation of endogenous IgG and transiently lowering IgG concentration. With this mechanism, efgartigimod alfa is expected to have therapeutic effects on gMG.

In Japan, clinical studies with efgartigimod alfa started in April 2018. The applicant concluded that the clinical studies including a global phase III study had demonstrated the efficacy and safety of efgartigimod alfa in the treatment of gMG, and has recently filed its marketing application.

Outside Japan, new drug applications for efgartigimod alfa were filed for the treatment of gMG in December 2020 in the US and in August 2021 in the EU, which are currently under review. As of September 2021, efgartigimod alfa has not been approved in any country or region.

Currently approved treatment options for gMG in Japan include corticosteroids (prednisolone,[1)] dexamethasone,[1)] etc.), calcineurin inhibitors (cyclosporine, tacrolimus hydrate),[1)] cholinesterase inhibitors (pyridostigmine bromide,[1)] ambenonium chloride,[1)] etc.), polyethylene glycol treated human normal immunoglobulin, and eculizumab.

1) These drugs have been approved for the treatment of "myasthenia gravis".

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Generation and control of cell substrate

A gene fragment was chemically synthesized based on the information about the IgG1 amino acid sequence where 5 mutated amino acids had been inserted into the known amino acid sequence of the human IgG1 Fc fragment, aiming to increase its binding affinity for human FcRn. Using this, a gene expression construct for efgartigimod alfa was generated. The gene expression construct was then transfected into a Chinese hamster ovary (CHO) cell line, and a clone most suitable for the manufacture of efgartigimod alfa was selected for the preparation of the master cell bank (MCB) and working cell bank (WCB).

The identity and purity of the MCB, WCB, and end of production cells bank (EOPC) were evaluated according to the ICH Q5A(R1), ICH Q5B, and ICH Q5D guidelines. The results demonstrated that all cell lines were genetically stable throughout the production of efgartigimod alfa, while detecting no cell line contamination with viral or nonviral adventitious agents other than endogenous retrovirus-like particles, which are commonly present in rodent cell lines.

The MCB and WCB are preserved in the vapor phase of liquid nitrogen. There are no plans for creating a new MCB, but a new WCB will be created as necessary.

2.1.2 Manufacturing process

The manufacturing process for the drug substance consists of the following steps: thawing of the WCB, expansion culture, production bioreactor culture, harvesting, [redacted] chromatography, viral inactivation ([redacted] treatment), [redacted] chromatography, [redacted] chromatography, viral filtration, concentration/diafiltration, mixing of excipients, and bulk filtration/filling/storage.

The critical steps are the [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted] steps.

For the manufacturing process of the drug substance, process validation is performed on a commercial scale.

2.1.3 Safety evaluation of adventitious agents

Except the CHO cells that are the host cells, no raw materials of biological origin are used in the process of manufacturing the drug substance.

Purity testing was performed on the MCB, WCB, and EOPC [see Section 2.1.1]. In addition, bioburden testing, bacterial endotoxin testing, mycoplasma testing, testing for minute virus of mice, *in vitro* adventitious virus testing, and transmission electron microscopy were performed on unprocessed/unpurified bulk before harvesting manufactured at a commercial scale. None of these tests revealed contamination with viral

or nonviral adventitious agents other than retrovirus-like particles commonly present in rodent cell lines. Other than transmission electron microscopy, these tests for the unprocessed/unpurified bulk before harvesting are designated as in-process control tests.

A viral clearance study with model viruses was conducted for the purification step and demonstrated a certain level of viral clearance capacity of the purification step (Table 1).

Table 1. Viral clearance study results

Manufacturing process	Viral clearance factor (log_{10})			
	Xenotropic murine leukemia virus	Pseudorabies virus	Reovirus type 3	Minute virus of mice
[redacted] chromatography	[redacted]	[redacted]	[redacted]	[redacted]
Viral inactivation ([redacted] treatment)	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] chromatography	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] chromatography	[redacted]	[redacted]	[redacted]	[redacted]
Viral filtration	[redacted]	[redacted]	[redacted]	[redacted]
Total viral clearance factor	≥23.66	≥22.24	≥19.57	10.55

a) Not used for determination of the total viral clearance factor.

2.1.4 Manufacturing process development

The major changes made to the manufacturing process during the development of the drug substance are shown below. (The manufacturing processes are referred to as Processes A, B, C, D, E, and F, and the proposed commercial process.) Phase I studies used the formulations produced from the drug substances manufactured by Process B or C, the phase II studies used the formulations produced from the drug substances manufactured by Process B, and the phase III studies used the formulations produced from the drug substances manufactured by Process C, D, E, or F.

- Process A → Process B: Changes in [redacted] and [redacted]
- Process B → Process C: [redacted]
- Process C → Process D: Changes in [redacted] used in the [redacted] step, [redacted] of the drug substance, etc.
- Process D → Process E: A change in [redacted]
- Process E → Process F: Changes in [redacted] and [redacted]
- Process F → Proposed commercial process: Changes in [redacted] in the [redacted] step, etc.

At each change in the manufacturing process, the comparability of quality attributes was assessed. The results demonstrated the comparability between the drug substances manufactured before and after the change.

A quality by design (QbD) approach was employed for the development of the manufacturing process [see Section 2.3].

2.1.5 Characterization

2.1.5.1 Structure and characterization

The drug substance was characterized as shown in Table 2.

Table 2. Characterization of the attributes of the drug substance

Primary/higher-order structure	Amino acid sequence, N- and C-terminal amino acid sequences, [redacted], glycation, post-translational modification [redacted], [redacted], [redacted], deamidation, [redacted], oxidation, glycosylation of [redacted]), disulfide bonds, free thiol group, and secondary and tertiary structures
Physicochemical properties	Molecular weight, size variants, and charge variants
Carbohydrate structure	N-linked oligosaccharide profile, [redacted] oligosaccharide profile, [redacted], and [redacted]
Biological properties	Binding affinity for human FcRn
	Inhibition of binding of huIgG3

The major biological properties of the drug substance were evaluated as follows:

- The binding affinity of efgartigimod alfa for human FcRn was determined using [redacted] and [redacted]-based [redacted] chromatography.
- The inhibitory activity of efgartigimod alfa against the binding of huIgG3 to human FcRn was determined using ELISA.

2.1.5.2 Product-related substances/Product-related impurities

Based on the results of the characterization tests, as described in Section 2.1.5.1, and other data, [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted] were identified as product-related substances, and Impurities A and B were identified as product-related impurities. Both of the product-related impurities are appropriately controlled according to the specifications for the drug substance and the drug product.

2.1.5.3 Process-related impurities

The process-related impurities include host cell proteins (HCPs), host cell-derived DNAs, Impurities C, D, E, and F, element impurities, bioburden, Impurity G, endotoxins, and Impurities H and I. All of these process-related impurities have been confirmed to be sufficiently removed during the manufacturing process. HCPs, host cell-derived DNAs, Impurity F, bioburden, and endotoxins are controlled according to the specifications for the drug substance.

2.1.6 Control of drug substance

The proposed specifications for the drug substance include content, description (color and clarity), identification (peptide mapping and potency), pH, purity (capillary gel electrophoresis with sodium dodecyl sulfate [CE-SDS] [reducing and nonreducing], gel permeation-high performance liquid chromatography [GP-HPLC], [redacted] high performance liquid chromatography [[redacted] HPLC], host cell-derived DNAs [quantitative polymerase chain reaction [PCR]], HCPs [ELISA], Impurity F [[redacted]]), endotoxins, charge variants (capillary isoelectric focusing [icIEF]), microbial limit, potency (competitive ELISA), and assay

(ultraviolet-visible spectrophotometry). [redacted] was added to the specifications for the drug substance during the review.

2.1.7 Stability of drug substance

Table 3 shows the main stability studies conducted on the drug substance.

Table 3. Main stability studies for the drug substance

	Number of batches[a)]	Storage conditions	Testing duration	Storage package
Long-term testing	3	-80˚C (≤-65˚C)	12 months[b)]	A high-density polyethylene bottle with a polypropylene screw cap
Accelerated testing	3	5 ± 3℃	12 months[b)]	
Stress testing	3	25 ± 2℃/60 ± 5%RH	12 months	
	3	40 ± 2˚C/≤25%RH	3 months	

a) The drug substance produced by the proposed commercial process was used.
b) The testing will be continued for 60 months.

The long-term testing and the accelerated testing showed no clear changes in the quality attributes throughout the testing periods.

The stress testing at [redacted]℃ showed a decrease in [redacted], an increase in [redacted] and a tendency for [redacted] to decrease, a decrease in [redacted], and a tendency for [redacted] to increase.

The stress testing at [redacted]℃ showed a decrease in [redacted], an increase in [redacted] and a tendency for [redacted] to decrease, a decrease in [redacted], and a tendency for [redacted] to decrease, a tendency for [redacted] to decrease and a tendency for [redacted] to increase, and a tendency for [redacted] to decrease.

Based on the results, a shelf-life of [redacted] months has been proposed for the drug substance, when stored at [redacted]℃ (≤[redacted]℃) in a high-density polyethylene bottle with a polypropylene screw cap.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is an aqueous injection in 20-mL glass vials, each of which provides a solution containing 400 mg of efgartigimod alfa. The drug product also contains monobasic sodium phosphate monohydrate, anhydrous disodium hydrogen phosphate, sodium chloride, L-arginine hydrochloride, polysorbate 80, and water for injection as excipients.

2.2.2 Manufacturing process

The manufacturing process for the drug product consists of thawing of the drug substance, mixing/filtration for bioburden reduction, sterile filtration/filling/testing, visual inspection, packaging/labeling/storage, and visual inspection/storage steps.

The critical steps are [redacted] and [redacted].

Process validation for the drug product was conducted on a commercial scale.

2.2.3 Manufacturing process development

The major changes in the manufacturing method made during the development stage for the drug product were changes in manufacturing site and manufacturing scale, etc. (the manufacturing processes before and after the changes are referred to as the previous manufacturing processes and the proposed manufacturing process, respectively). In the clinical studies, drug products produced by the previous manufacturing processes were used.

At each change in the manufacturing process, the quality attributes were assessed for compatibility, and the results demonstrated that the drug products manufactured before and after the change were comparable.

A QbD approach was employed for the development of the manufacturing process [see Section 2.3].

2.2.4 Control of drug product

The proposed specifications for the drug product include content, description (color and clarity), identification (icIEF and potency), osmolarity, pH, purity (CE-SDS [reducing and nonreducing], GP-HPLC, and [redacted] HPLC), endotoxins, extractable volume, foreign insoluble matter, insoluble particulate matter, sterility, charge variants, potency (competitive ELISA), and assay (ultraviolet-visible spectrophotometry).

2.2.5 Stability of drug product

The main stability studies of the drug product are shown in Table 4.

Table 4. Main stability studies for the drug products

	Manufacturing process	No. of batches	Storage conditions	Testing duration	Storage package
Long-term testing	Proposed commercial process[a)]	3	5 ± 3°C	12 months[c)]	A glass vial with an EFTE-laminated butyl rubber stopper
Accelerated testing	Proposed commercial process[a)]	3	25 ± 2°C/60 ± 5%RH	12 months	
Stress testing	Proposed commercial process[a)]	3	40 ± 2°C/75 ± 5%RH	6 months	
Photostability testing	A previous manufacturing process[b)]	1	Overall illumination ≥1.2 million lux·h and total near ultraviolet energy ≥200 w·h/m^2, 5 ± 3°C		

a) The drug substance produced by the proposed commercial process was used.
b) The drug substance produced by Process F was used. c) The stability study will be continued for 60 months.

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

The accelerated testing showed a tendency for [redacted] to decrease and a tendency for [redacted] to increase, a decrease in [redacted], a tendency for

[redacted] to decrease, a decrease in [redacted], an increase in [redacted] and a tendency for [redacted] to decrease, and a tendency for [redacted] to decrease.

The stress testing showed a decrease in [redacted] and an increase in [redacted], a decrease in [redacted], a decrease in [redacted], a decrease in [redacted], an increase in [redacted] and a tendency for [redacted] to decrease, and a decrease in [redacted].

The photostability testing showed that the drug product was unstable in light.

Based on the above results, a shelf-life of 12 months was proposed for the drug product when stored at 2°C to 8°C in a primary container consisting of a glass vial with an ethylene-tetrafluoroethylene co-polymer (EFTE)-laminated butyl rubber stopper and protected from light in a paper carton.

2.3 QbD

A QbD approach was employed for the development of the drug substance and the drug product. Quality control strategies were established through the following assessments, etc.

- Identification of critical quality attributes (CQAs)
  For the assessment of the quality of product-related impurities, process-related impurities, and general quality attributes, the following CQAs were identified based on the information collected during the development of efgartigimod alfa and relevant knowledge.
  CQAs: Description (color and clarity); pH; osmolarity; polysorbate 80 concentration; extractable volume; foreign insoluble matter; insoluble particulate matter; protein concentrations; potency; equivalence; purity; Impurities H, I, and G; microbial limit; sterility; endotoxins; pyrogens; integrity of the container closure system; aggregates; fragments; cysteine residues (free cysteine and disulfide bonds); HCPs; host cell-derived DNAs; and Impurity F
- Process characterization
  As a result of a process characterization risk assessment, the risks involved in each process parameter were ranked to identify the input variables (critical process parameters) and output variables (performance attributes) that have important impacts on the CQAs or the process performance.
- Establishment of the control procedures
  Based on knowledge about the process including the results of the above process characterization, and the results of batch analyses and stability studies, the control procedures for the quality attributes of efgartigimod alfa, consisting of a combination of the control of the process parameters and performance attributes, in-process control, and specifications, were established [for the control of product-related impurities and process-related impurities, see Sections 2.1.5.2 “Product-related substances/Product-related impurities” and 2.1.5.3 “Process-related impurities”].

2.R Outline of the review conducted by PMDA

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

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

The non-clinical pharmacology data submitted include the results from primary pharmacodynamics studies, secondary pharmacology studies, safety pharmacology studies, and a pharmacodynamic drug interaction study. Unless otherwise specified, *in vivo* studies used phosphate-buffered saline (PBS) as vehicles. The results of key studies are described below.

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies

3.1.1.1 Cross-reactivity with FcRns

The cross-reactivities of efgartigimod alfa and those of human wild-type Fc fragment with FcRns from various animal species and humans were evaluated at pH 6.0 and 7.4 using surface plasmon resonance (SPR) and ELISA. The results are shown in Table 5 (CTD 4.2.1.1-1, CTD 4.2.1.1-2). Under both acidic and neutral conditions, the binding affinity of efgartigimod alfa for animal and human FcRns was higher than that of human wild-type Fc fragment.

Table 5. Binding affinity of efgartigimod alfa and human wild-type Fc fragment for animal and human FcRns

		SRP (K_d value) (nmol/L)		ELISA (EC_{50} value) (ng/mL)	
	pH	Efgartigimod alfa	Human wild-type Fc fragment	Efgartigimod alfa	Human wild-type Fc fragment
Mouse	6.0	0.01 ± 0.01	1.04 ± 0.29	3.79	4.95
	7.4	0.64 ± 0.11	-	3.21	1182
Rat	6.0	0.53 ± 0.11	7.54 ± 0.93	3.80	17.18
	7.4	1.89 ± 0.35	-	3.89	-
Rabbit[a)]	6.0	6.37	36.0		
	7.4	301	-		
Swine	6.0	0.35 ± 0.05	1.76 ± 0.61	8.25	16.1
	7.4	11.70 ± 2.03	-	9.84	8683
Dog	6.0	0.19 ± 0.05	36.02 ± 13.60	5.46	58.52
	7.4	1.74 ± 0.19	-	4.01	-
Monkey	6.0	0.23 ± 0.18	55.15 ± 23.20	6.68	1532
	7.4	14.49 ± 2.77	-	8.62	-
Human	6.0	0.35 ± 0.06	27.99 ± 6.20	6.04/5.67[b)]	651.7/660.1[b)]
	7.4	8.59 ± 1.35	-	7.32/7.00[b)]	-/-[b)]

Mean ± SD; -, Due to low or no binding to FcRn, no K_d or EC_{50} value could be determined.

a) The SPR study with rabbit FcRn (CTD 4.2.1.1-2) was conducted separately from the SPR study with other animal and human FcRns (CTD 4.2.1.1-1). The corresponding K_d values of efgartigimod alfa and human wild-type Fc fragment for human FcRn in the SPR experiment with rabbit FcRn (CTD 4.2.1.1-2) were 8.63 and 23.0 nmol/L at pH 6.0, and 31.0 nmol/L and indeterminable (due to low binding) at pH 7.4, respectively. No ELISA study was conducted to determine binding affinity for rabbit FcRn.

b) Individual values from 2 experiments

Efgartigimod alfa 25 or 50 μg/mL was added to frozen human and monkey tissues to evaluate tissue cross-reactivity using immunohistochemical staining. Staining was observed in endothelial cells and the cytoplasm of multiple human and monkey tissues, as well as the mucous membranes of the bladder, stomach, and small intestine, lymph node sinus histiocytes, and splenic sinusoidal endothelial cells in humans, and thyroid

follicular cells, lymph node sinus histiocytes, and splenic sinusoidal endothelial cells in monkeys (CTD 4.2.1.1-3).

3.1.2 *In vivo* studies

3.1.2.1 Effects of modified test molecules on endogenous IgG (CTD 4.2.1.1-4)

To evaluate the effects of test molecules [2)] that had been modified to increase binding affinity for FcRn, monkeys received an intravenous bolus[3)] of a tracer antibody at 1 mg/kg, followed 5 minutes later by a continuous intravenous infusion of efgartigimod alfa 7 mg/kg, ABDEG-hIgG1[2)] 20 mg/kg, NHance-Fc[2)] 7 mg/kg, or the vehicle,[3)] and change over time in serum tracer antibody concentration was investigated. The NHance-Fc group had no change in serum tracer antibody concentration, as compared with the vehicle group, whereas serum tracer antibody concentration rapidly declined in the efgartigimod alfa (human IgG1 fragment engineered with ABDEG mutations[4)]) group and the ABDEG-hIgG1 (full-length human IgG1 engineered with ABDEG) group. The efgartigimod alfa group and the ABDEG-hIgG1 group had decreased endogenous IgG concentrations to a similar degree as compared with the vehicle group. The applicant explained that efgartigimod alfa, which had no antigen-binding fragment (Fab), may be less likely to bind non-specifically than ABDEG-hIgG1.

3.1.2.2 Effects on mouse and rat endogenous IgG (CTD 4.2.1.1-5)

A single intravenous dose of efgartigimod alfa 2, 20, or 100 mg/kg was administered to mice, and blood samples were taken predose, and 1 and 24 hours, and 2, 4, 7, and 14 days postdose to evaluate change over time from predose in total serum IgG concentration. The decrease in serum IgG concentration by efgartigimod alfa began at 2 mg/kg and became almost constant at ≥20 mg/kg, with a maximum decrease from predose to 2 days postdose of 66% at 100 mg/kg.

A single intravenous dose of efgartigimod alfa 2, 20, or 100 mg/kg was administered to rats, and blood samples were taken predose, and 1 and 24 hours, and 2, 4, 7, and 14 days postdose to evaluate change over time from predose in total serum IgG concentration. Serum IgG concentration did not change at 2 mg/kg but decreased at ≥20 mg/kg, with a maximum decrease from predose to 2 days postdose of 48% at 100 mg/kg.

3.1.2.3 Effects on rabbit endogenous IgG (CTD 4.2.1.1-9)

A total of 23 once-daily intravenous doses of efgartigimod alfa 10, 30, or 100 mg/kg/day, or the vehicle (physiological saline) were administered to pregnant rabbits between gestation days 6 and 28. Blood samples were collected predose and 1 hour postdose on gestation days 6, 16, and 26, predose on gestation days 9, 13, 20, and 23, and gestation day 29 to evaluate the change over time from predose in serum IgG concentration.

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2) The following test molecules were used:
- Efgartigimod alfa: An Fc fragment, where ABDEG mutations (M252Y, S254T, T256E, H433K, and N434F) were inserted into the amino acid residues at positions 221 to 447 of human IgG1 to increase binding affinity for FcRn at pH 6.0 and pH 7.0
- ABDEG-hIgG1: A full-length human IgG1 antibody, where ABDEG mutations (M252Y, S254T, T256E, H433K, and N434F) were inserted into human IgG1
- NHance-Fc: An Fc fragment, where NHance mutations (H433K and N434F) were inserted into the amino acid residues at positions 221 to 447 of human IgG1 to increase binding affinity for FcRn at pH 6.0 (*Curr Top Microbiol Immunol*. 2014;382:249-72)

3) Blood samples were taken 1 day and 0 hours predose, and 5 minutes, 2 and 6 hours, and 2, 3, 4, 5, 6, 8, 10, and 12 days postdose.

4) An Fc fragment, where the amino acid residues at positions 221 to 447 of human IgG1were substituted (M252Y, S254T, T256E, H433K, and N434F) to increase binding affinity for FcRn at pH 6.0 and pH 7.0

After the administration of efgartigimod alfa 10, 30, and 100 mg/day, serum IgG concentrations decreased by ≤53%, ≤62%, and ≤69% on 7, 10, and 7 days postdose, respectively, as compared with predose.

3.1.2.4 Effects on monkey endogenous IgG (CTD 4.2.1.1-6)

Monkeys received an intravenous bolus of a tracer antibody at 1 mg/kg, followed 48 hours later by a continuous intravenous infusion of efgartigimod alfa 0.2, 2, 20, or 200 mg/kg, or the vehicle,[5)] and serum tracer antibody concentrations and serum IgG concentrations were determined. Serum tracer antibody concentration did not change with efgartigimod alfa at 0.2 mg/kg but decreased at ≥2 mg/kg. Serum IgG concentration did not change at 0.2 or 2 mg/kg but decreased at a constant degree at ≥20 mg/kg, with a maximum decrease from predose of 55% at 5 days postdose.

Efgartigimod alfa 20 mg/kg was administered to monkeys once daily for 4 consecutive days (consecutive administration)[6)] or once every 4 days for 4 times (intermittent administration)[7)] to evaluate change over time from predose in serum IgG concentration. The consecutive administration and the intermittent administration showed similar changes in serum IgG concentration during the early period of treatment. However, the decrease in serum IgG concentration from Day 7 of treatment and thereafter was greater in the intermittent administration group than in the consecutive administration group. The decrease in serum IgG concentration in the consecutive administration group was similar to that observed after a single intravenous dose of efgartigimod alfa, while the intermittent administration resulted in a longer-lasting decrease in serum IgG concentration than in the consecutive administration, with a maximum decrease from predose of approximately 75%.

3.1.2.5 A study in a rat model of anti-acetylcholine receptor antibody-positive myasthenia gravis (AChR-MG) (CTD 4.2.1.1-8)

An intraperitoneal dose of efgartigimod alfa 50 mg/kg or the vehicle was administered to an AChR-MG model in rats,[8)] and at 2 and 24 hours later, a rat anti-acetylcholine (anti-AChR) antibody was administered. After that, the clinical score[9)] and grip strength[10)] were assessed and serum IgG concentrations were determined.[11)] Clinical deterioration and the decrease in grip strength peaked at 48 to 54 hours after anti-AChR antibody administration in both the efgartigimod alfa group and the vehicle group, while the decline in clinical score lessened at 30, 54, and 72 hours after anti-AChR antibody administration, and the decrease in grip strength attenuated at 72 hours in the efgartigimod alfa group as compared with the vehicle group. The decrease from predose in serum IgG concentration peaked at approximately 74% at 72 hours postdose in the efgartigimod group.

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5) Blood samples were taken 3 days and 0 hours predose, and 0, 2, 6, 24, 48, and 72 hours, and 5, 7, 10, 14, 17, 21, 24, and 28 days postdose.
6) On Days 1 to 4 of treatment, blood samples were taken predose, and 0 and 24 hours, and 6, 7, 8, 10, 12, 14, 17, 21, 24, 28, 31, 35, 38, and 42 days postdose.
7) For each dose, blood samples were taken predose, and 0, 2, 6, 24, 48, and 72 hours, and 17, 21, 24, 28, 31, 35, 38, and 42 days postdose.
8) The model was prepared by intraperitoneally administrating rat anti-AChR antibody at 1 mg/kg to rats.
9) The clinical score was rated on a scale of 0 to 4 (0, no symptoms; 1, decreased grip strength/easy fatigability; 2, generalized weakness/hunched position/decreased body weight/tremor; 3. severe weakness/moribund; and 4. death).
10) Grip strength was assessed 24 hours before, and 0, 6, 24, 30, 48, 54, and 72 hours after the administration of an anti-AChR antibody.
11) Blood samples were taken 24 and 2 hours before, and 24, 48, and 72 hours after the administration of an anti-AChR antibody.

3.1.2.6 A study in a mouse model of anti-muscle specific receptor tyrosine kinase antibody-positive MG (MuSK MG) (CTD 4.2.1.1-7)

To a mouse model of MuSK-MG,[12] efgartigimod alfa 1 mg/body/day or the vehicle was administered once-daily intraperitoneally from Day 4 of treatment with a patient-derived IgG total fraction. Blood samples were taken every 3 days, and muscle function assessments including the measurement of grip strength and suspension time were conducted until Day 15. In the efgartigimod alfa group, the anti-MuSK antibody titer decreased after the start of treatment with efgartigimod alfa but increased again around Day 10 of treatment with the patient-derived IgG total fraction, indicating that the decrease in IgG due to efgartigimod alfa had attenuated. Grip strength and suspension time decreased in the later stage of the study period in the vehicle group, while suspension time decreased at the initial assessment, but grip strength became stable and suspension time recovered thereafter in the efgartigimod alfa group.

To a mouse model of MuSK-MG,[13] efgartigimod alfa 0.5 mg/body/day or human wild-type Fc fragment at 0.5 mg/body/day was administered once-daily intraperitoneally from Day 5 of treatment with patient-derived IgG4, and muscle function assessments including the measurement of grip strength and suspension time were conducted. In the human wild-type Fc fragment group, a persistent decrease in grip strength was observed from Day 5 of treatment with patient-derived IgG4, while the decreased grip strength recovered in the efgartigimod alfa group. After the completion of the study, an e*x vivo* diaphragmatic electromyography in the MuSK-MG mouse model revealed that the decrease in sensitivity of the diaphragm to d-tubocurarine (125 nmol/L), when persistent muscle contraction was induced, was higher in the human wild-type Fc fragment group than in the efgartigimod alfa group.

3.2 Secondary pharmacodynamics

3.2.1 *In vitro* studies

3.2.1.1 Binding affinity for Fc gamma receptors (FcγRs) and complement protein 1q (C1q) (CTD 4.2.1.1-1)

The binding affinities of efgartigimod alfa and human wild-type Fc fragment for human FcγRs were evaluated using ELISA. The results are shown in Table 6.

Table 6. Binding affinities of efgartigimod alfa and human wild-type Fc fragment for human FcγRs (EC_{50} values)

	Efgartigimod alfa	Human wild-type Fc fragment
FcγRIIIa (hCD16a)	47.71	15.00
FcγRIIa (hCD32a)	232.5	62.56
FcγRIIb (hCD32b)	82424	144.7
FcγRI (hCD64)	0.1154	0.08043

Mean (nmol/L)

The binding affinities of efgartigimod alfa and human wild-type Fc fragment for human C1q were assessed using ELISA. The results provided EC_{50} values of 9.9 and 14.7 nmol/L, respectively.

[12] An IgG total fraction (1.84 g/kg/day) purified from patients with MuSK antibody-positive MG was intraperitoneally administered once daily for 14 days.

[13] A subclass 4 IgG (0.15 g/kg/day) purified from patients with MuSK antibody-positive MG was intraperitoneally administered once daily for 11 days.

3.2.1.2 Activation of natural killer (NK) cells (CTD 4.2.1.1-1)

Human NK cells were incubated with efgartigimod alfa 50 μg/mL or human wild-type Fc fragment, and the CD107a-positive cell count, an indicator of activated NK cells, was determined after 4 and 24 hours to evaluate the activation of NK cells by efgartigimod alfa. The percentages of CD107a-positive NK cells were <0.5% in the efgartigimod alfa group and the human wild-type Fc fragment group, as compared with 9% to 12% in the positive control[14)] group, suggesting that efgartigimod alfa did not induce NK cell activation.

3.2.2 *In vivo* studies

3.2.2.1 Effects on albumin, and endogenous IgA and IgM

A continuous intravenous dose of efgartigimod alfa 7 mg/kg, ABDEG-hIgG1[2)] 20 mg/kg, NHance-Fc[2)] 7 mg/kg, intravenous immunoglobulin (IVIg) 2 g/kg, or the vehicle was administered to monkeys,[15)] and albumin concentrations were determined predose, and 3, 17, and 40 days postdose. The albumin concentration did not differ from that in the vehicle group in any treatment groups (CTD 4.2.1.1-4).

Monkeys received an intravenous bolus of a tracer antibody at 1 mg/kg, followed 48 hours later by a continuous intravenous infusion of efgartigimod alfa 200 mg/kg or the vehicle, and serum IgA and IgM concentrations before, and 24 hours, and 5, 7, and 21 days after the intravenous infusion of efgartigimod alfa or the vehicle were determined. The results showed no differences in the percent change in serum IgA or IgM concentration between the efgartigimod alfa 200 mg group and the vehicle group (CTD 4.2.1.1-6).

3.3 Safety pharmacology

Table 7 presents a summary of the safety pharmacology study results. The effects of efgartigimod alfa on the cardiovascular system were evaluated as part of the 4- and 26-week repeated dose toxicity studies in cynomolgus monkeys.

14) An Fc fragment that had >100-fold higher binding affinity for FcγRIIIa than did PBS, which served as the negative control

15) From Day 14 of treatment, the test substances, with the exception of IVIg were administered at doses that were 3 times the above doses, and efgartigimod alfa 70 mg/kg was administered to the vehicle group.

Table 7. Summary of safety pharmacology study results

Parameter	Test system	Observations/ examinations	Dose	Route of administration	Findings	CTD
Central nervous and respiratory systems	Cynomolgus monkeys (2/sex/group)	FOB, respiratory rate, and body temperature	0,[a] 10, 30, or 100 mg/kg once weekly for 5 weeks	Intravenous	No effects	4.2.1.3-1
Cardiovascular system	Cynomolgus monkeys (3/sex/group)	Electrocardiogram, heart rate, and blood pressure	0,[b] 10, 30, 50, or 100 mg/kg as a single dose	Intravenous	No effects	4.2.3.1-1
	Cynomolgus monkeys (3/sex/group)		0,[b] 3, 30, or 100 mg/kg every 2 days for 4 weeks	Intravenous	No effects	4.2.3.2-2
	Cynomolgus monkeys (4/sex/group)		0,[b] 10, 30, or 100 mg/kg once weekly for 26 weeks	Intravenous	No effects	4.2.3.2-3

a) A vehicle containing 25 mmol/L phosphate, 100 mmol/L sodium chloride, 150 mmol/L L-arginine hydrochloride, and 0.02% (w/v) polysorbate 80 (pH 6.7)
b) Physiological saline

3.4 Pharmacodynamic drug interactions (CTD 4.2.1.4-1)

The pharmacokinetics of efgartigimod alfa, when administered simultaneously with IVIg (simultaneous administration) or 2 days before the administration of IVIg (sequential administration), was evaluated in transgenic humanized FcRn (Tg32) mice.[16] Human IgG 200 mg/kg and a tracer antibody 15 mg/g were intravenously administered, and 2 days later, efgartigimod alfa 20 mg/kg, human wild-type Fc fragment 20 mg/kg (the isotype control), or the vehicle was simultaneously administered with IVIg (human IgG) 2 g/kg (simultaneous administration). Blood samples were taken 2 days and 1 hour predose, and 1 and 7 hours, and 1, 2, 3, 4, 7, and 14 days postdose to determine the plasma concentrations of efgartigimod alfa, human IgG, and the tracer antibody using ligand binding assays. Similarly, the pharmacokinetics of efgartigimod alfa administered 2 days before the administration of IVIg (sequential administration) was evaluated. The results showed that the pharmacokinetics of efgartigimod alfa is not affected by different dose timings of efgartigimod alfa and IVIg. In contrast, the human IgG concentration increased immediately after the simultaneous administration, and rapidly declined to near the baseline 2 to 3 days after administration. In addition, in rats receiving the sequential administration, the human IgG concentration decreased after the administration of efgartigimod alfa but was maintained above a baseline level by the administration of IVIg until 12 days after the administration of efgartigimod alfa, and tended to return to near the baseline 14 days after the administration of efgartigimod alfa.

3.R Outline of the review conducted by PMDA

3.R.1 Mechanism of action of efgartigimod alfa

PMDA asked the applicant to explain the pathogenesis of MG and the action mechanism of efgartigimod alfa.

The applicant's explanation:

- At the neuromuscular junction, acetylcholine released from the nerve terminal binds to AChR, which is highly expressed on the muscle cell membrane, thereby inducing muscle contraction. Agrin released from nerves binds to LRP4 to form a complex that activates MuSK, leading to dense AChR localization (*Nat Rev Dis Primers.* 2019;5:30), which is essential for signaling at the neuromuscular junction.

16) Tg32 mice, which express human FcRn but no endogenous mouse FcRn, are used for the characterization of binding to human FcRn. In the mice, endogenous mouse IgG concentrations are lower, because mouse IgG has a low binding affinity for human FcRn, and mouse IgG is not recycled by human FcRn.

- MG is an autoimmune disease mediated by pathogenic IgG autoantibodies that target the components of the postsynaptic membrane at the neuromuscular junction. The major molecules that are the target of these IgG autoantibodies at the neuromuscular junction are AChR, MuSK, and LRP4.
- Approximately 90% of patients with MG carry autoantibodies in serum, while the remaining 10% of patients may have autoantibodies that are either unknown or undetectable due to the limitations in the assay (e.g., below the lower limit of detection) (*N Engl J Med.* 2016;375:2570-81, *Brain.* 2008;131:1940-52). The most common autoantigen is AChR, and approximately 80% of patients with MG carry anti-AChR antibodies. Anti-MuSK antibodies are detectable in approximately 1% to 10% of patients with MG (*Nat Rev Neurol*. 2016;12:259-68). Anti-LRP4 antibodies are not routinely measured, and the variety in assays used for detection and populations studied preclude the determination of exact percentage of anti-LRP4 antibody carriers.
- Anti-AChR antibodies functionally block AChR, accelerate cell entry and the decomposition of AChR, and activate complements. These actions decrease the density of functional AChR and simplify the structure of the neuromuscular junction, thereby impairing neuromuscular transmission (*N Engl J Med.* 2016;375:2570-81). Anti-AChR antibodies are predominantly in the IgG subclasses 1 and 3 (*Clin Exp Immunol.* 1987;67:82-8).
- Anti-MuSK antibodies block the interactions between MuSK and LRP4 or that between MuSK and collagen Q, inhibit the activation of MuSK, and thereby decrease AChR density at the postsynaptic membrane and disrupt signaling (*Proc Natl Acad Sci USA.* 2013;110:20783-8). Anti-MuSK antibodies are known to be predominantly in IgG subclass 4. No complement deposits are found at the neuromuscular junction in anti-MuSK antibody-positive patients (*Ann Neurol*. 2004;55:580-4; *Japanese Clinical Guidelines for Myasthenia Gravis 2014*. Nankodo Co., Ltd., 2014).
- The pathogenicity of anti-LRP4 antibodies has been implicated since MG-like symptoms were shown to be induced in an animal model generated by administrating IgGs purified from LRP4-immunized animals. Anti-LRP4 antibodies block the binding of agrin to LRP4 and inhibit agrin-dependent MuSK activation, thereby affecting AChR clustering *(J Clin Invest.* 2013;123:5190-202, *Exp Neurol.* 2017;297:158-67). Anti-LRP4 antibodies primarily belong to the IgG subclasses 1 and 2, and the involvement of complement activation in the pathogenicity of anti-LRP4 antibodies has been implied (*Can J Neurol Sci.* 2018;45:62-7). However, whether anti-LRP4 antibodies impair neuromuscular transmission in patients with MG has yet to be fully clarified (*Japanese Clinical Guidelines for Myasthenia Gravis 2014*. Nankodo Co., Ltd., 2014).
- There is a report that autoantibodies are undetectable by routine assays in approximately 10% of patients with gMG (*Nat Rev Neurol.* 2016;12:259-68). Even patients with gMG who have anti-AChR antibodies may have been diagnosed as anti-AChR antibody-negative and anti-MuSK antibody-negative due to limitation in assay systems, etc. Some patients with gMG have autoantibodies targeting other components of the neuromuscular junction such as collagen Q and agrin, and they may be anti-AChR antibody- or anti-MuSK antibody-positive or -negative. Thus, the clinical significance of autoantibodies other than anti-AChR antibodies or anti-MuSK antibodies and their importance as the pathogenesis of gMG remain unclear (*Nat Rev Dis Primers.* 2019;5:30, *Front Immunol.* 2020;11:212).
- FcRn is involved in IgG transport and homeostasis (*Curr Top Microbiol Immunol.* 2014;382:249-72). IgG enters endothelial cells through pinocytosis and binds to FcRn in endosomes under acidic conditions (pH

≤6.5). The IgG bound to FcRn is thus not decomposed by lysosome but is transferred to the cell surface, separated from the IgG-FcRn complex in intercellular spaces under neutral conditions (at approximately pH 7.4) to be released into the circulating blood or to undergo transcytosis to other tissues for recycling. Due to this FcRn-mediated recycling, IgG has a half-life as long as approximately 21 days, while other serum proteins that are not recycled through FcRn, such as IgM, IgE, IgA, and IgD, have half-lives of approximately 5 to 6 days. This is one reason that IgG is present in the plasma at high concentrations (*Front Immunol.* 2019;10:1540).

- Efgartigimod alfa is an FcRn-targeted human IgG1 antibody Fc fragment with modified amino acid residues, which has been shown *in vitro* to have higher binding affinity for FcRn than human wild-type Fc fragment under both acidic and neutral conditions [see Section 3.1.1.1]. When added to frozen human and monkey tissues to evaluate its tissue cross-reactivity using immunohistochemical staining [see Section 3.1.1.1], the staining pattern of efgartigimod alfa was consistent with a report that FcRn, the target of efgartigimod alfa, is expressed in endothelial cells and tissue-resident macrophages (*J Histochem Cytochem.* 2017:65;321-33), suggesting that efgartigimod alfa is unlikely to bind to epitopes outside the target site.[17)]
- Efgartigimod alfa decreased serum IgG concentration in monkeys [see Section 3.1.2.4]. In animal model studies, efgartigimod alfa decreased endogenous IgG concentration and improved MG-like symptoms such as lowered grip strength [see Sections 3.1.2.5 and 3.1.2.6]. In a study in MuSK-MG model mice, the anti-MuSK antibody titer decreased transiently but then increased again, suggesting attenuated effect of efgartigimod alfa to lower the IgG concentration [see Section 3.1.2.6]. This was attributable to the saturation of FcRn-mediated IgG recycling during the study due to daily doses of IgG purified from anti-MuSK antibody-positive patients.
- Based on these observations, efgartigimod alfa is expected to exert its therapeutic effect on gMG by competitively blocking the binding of endogenous IgG to FcRn and inhibiting FcRn-mediated IgG recycling, leading to the promotion of IgG degradation and a decrease in the concentrations of any subclasses of IgG antibodies, including pathogenic IgG autoantibodies.

PMDA asked the applicant to explain possible adverse events characteristic of efgartigimod alfa, in views of its action mechanism different from that of existing gMG medications and pharmacological actions.

The applicant's explanation about the action mechanisms of existing gMG treatments (corticosteroids, noncorticosteroidal immunosuppressants such as calcineurin inhibitors, IVIg, hemocatharsis, and eculizumab), cholinesterase inhibitors that are supplementally administered in the treatment of gMG, and efgartigimod alfa:

- Corticosteroids and nonsteroidal immunosuppressants such as calcineurin inhibitors exert their nonspecific immunosuppressive effects through various mechanisms, including the inhibition of B cell and T cell activation (*Allergy Asthma Clin Immunol.* 2013;9:30, *Neuropsychiatr Dis Treat.* 2011;7:151-60).

17) Because no staining was observed in the liver or kidney, where FcRn had been reported to be expressed. Albeit undeniable low stainability of the staining method used in the study for FcRn in some tissues, histopathological findings from the 26-week repeated dose toxicity study in monkeys (CTD 4.2.3.2-3), etc. did not reveal any evident change that was considered to be associated with treatment with efgartigimod alfa in tissues other than the target sites of efgartigimod alfa. Based on these results, the applicant explained that efgartigimod alfa would be unlikely to bind to epitopes outside its target site.

- Although the action mechanism of IVIg has yet to be fully clarified, a report indicates that IVIg may exert its effects through the inhibition of macrophage Fc receptors, the suppression of complement activation, and the neutralization of antibody and cytokine formation (*Neurologist.* 2015;19:145-8). Another possible mechanism is that a high concentration of IgG in the circulatory blood after massive doses of immunoglobulin leads to the saturation of FcRn-mediated IgG recycling, and thereby promotes the degradation of endogenous IgG antibodies including pathogenic autoantibodies (*Ther Adv Neurol Disord.* 2021;14:1-7).
- Hemocatharsis, an extracorporeal circulatory treatment that removes plasma and its components from the circulating blood, exerts its therapeutic effect by removing pathogenic IgG autoantibodies and complement molecules (*Nat Rev Dis Primers.* 2019;5:30).
- Eculizumab, a monoclonal antibody directed against complement protein C5, exerts its therapeutic effect by binding specifically to complement C5, preventing its cleavage to C5a and C5b, thereby inhibiting anti-AChR antibody-mediated complement activation that is presumed to play a role in the pathogenesis of MG (*Lancet Neurol.* 2017;16:947-8).
- Cholinesterase inhibitors inhibit the degradation of acetylcholine and increase acetylcholine concentration at the neuromuscular junction, thereby enhancing muscle contraction (*Japanese Clinical Guidelines for Myasthenia Gravis 2014*. Nankodo Co., Ltd., 2014).
- Efgartigimod alfa inhibits FcRn-mediated IgG recycling and reduces IgG antibodies including pathogenic IgG autoantibodies.

The applicant's explanation about adverse events that may develop specifically in association with the use of efgartigimod alfa, in terms of the pharmacological actions:

Efgartigimod alfa transiently decreases all IgG subclasses through its action mechanism and can therefore cause infections due to decreased immunoglobulins. Thus, efgartigimod alfa is likely to increase the risk of infections. The clinical studies however showed, despite the tendency toward slightly increased incidence of infection-related adverse events in the efgartigimod alfa group as compared with the placebo group, most of the events reported in the efgartigimod alfa group were mild or moderate in severity, and none were serious adverse events for which a causal relationship to efgartigimod alfa could not be ruled out.

PMDA's view:
The applicant has reasonably explained the action mechanism of efgartigimod alfa from a viewpoint of its pharmacological actions based on the currently available knowledge. The efficacy and safety of efgartigimod alfa are to be further discussed in Sections 7.R.2 and 7.R.3, respectively.

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

As non-clinical pharmacology data of efgartigimod alfa, the applicant submitted data on the absorption and excretion of intravenous efgartigimod alfa from pharmacokinetics studies in mice, rabbits, and monkeys, and a toxicokinetic evaluation conducted as part of the toxicity studies in rats, rabbits, and monkeys. Meanwhile, efgartigimod alfa is a human IgG1 antibody Fc fragment, and is thought to be distributed in the same manner

as endogenous IgG1 antibody fragments and degraded to small peptides and amino acids similarly to endogenous IgG in the body. Thus no distribution or metabolism study results were submitted. Serum efgartigimod alfa concentrations were measured using sandwich ELISAs with a lower limit of quantification of from 2.5 to 250 ng/mL, and urinary efgartigimod alfa concentrations using sandwich ELISAs with a lower limit of quantification of from 80 to 100 ng/mL. Serum anti-drug antibody (ADA) concentrations were determined using bridging ELISAs or affinity capture elution (ACE) bridging ELISAs. The results of main studies are described in the following subsections.

4.1 Absorption

4.1.1 Single-dose studies

Table 8 shows the serum pharmacokinetic parameters of efgartigimod alfa administered as a single intravenous bolus in female rabbits and male monkeys. Both animals in all dose groups tested positive for ADAs (Reference CTD 4.2.2.2-1, CTD 4.2.2.2-2).

Table 8. Pharmacokinetic parameters of efgartigimod alfa following a single intravenous bolus in female rabbits and male monkeys

Animal species	Dose (mg/kg)	Sex	N	C_{max} (μg/mL)	$t_{1/2}$ (h)	$AUC_{0\text{-t last}}$ (μg·h/mL)	Vss (mL/kg)	CTD
Rabbit	2	Female	3	26 ± 1	49.5 ± 4.3	934 ± 144		Reference CTD 4.2.2.2-1
	20	Female	3	296 ± 43	46.3 ± 8.8	10281 ± 1980		
	100	Female	3	1495 ± 63	37.0 ± 4.2[a)]	43424 ± 1454		
Monkey	20[b)]	Male	3	638 ± 84.4	42.8 ± 7.2	9484 ± 959	125 ± 20.9	4.2.2.2-2
	20[c)]	Male	3	554 ± 37.6	44.7 ± 2.0	10741 ± 1744	127 ± 6.5	

Mean ± SD
a) The $t_{1/2}$ value adjusted for the prolongation in the α phase due to the increase in dose was 45.9 ± 6.9 hours.
b) [redacted]-derived formulation; c) [redacted]-derived formulation

4.1.2 Repeated-dose studies (toxicokinetics)

In the 4-week repeated intravenous dose toxicity study in male and female rats, the embryo-fetal development study in female rabbits, and the 26-week repeated intravenous dose toxicity study in male and female monkeys, the toxicokinetics of efgartigimod alfa administered as repeated intravenous doses were evaluated. Table 9 shows the serum pharmacokinetic parameters of efgartigimod alfa. In the repeated dose toxicity studies in rats and monkeys, ADA concentrations were determined. In rats, 3 of 18 animals in the 10 mg/kg group, 3 of 18 animals in the 30 mg/kg group, and 2 of 18 animals in the 100 mg/kg group tested positive for ADAs. In monkeys, all animals tested positive for ADAs (CTD 4.2.3.2-1, CTD 4.2.3.5.2-4, CTD 4.2.3.2-3).

Table 9. Pharmacokinetic parameters of efgartigimod alfa following repeated intravenous doses in male and female rats, female rabbits, and male and female monkeys

	Route of administration	Treatment duration	Dose (mg/kg)	Timepoint	Sex	N	C_{max} (μg/mL)	$t_{1/2}$ (h)	AUC (μg·h/mL)	CTD
Rat	Intravenous (bolus)	4 weeks (every 2 days)	10	Day 1	Male	3[a)]	627.7		94202 [b)]	4.2.3.2-1
					Female	3[a)]	659.9		89823 [b)]	
				Day 29	Male	3[a)]	357.7	17	8598.2 [c)]	
					Female	3[a)]	377.9	45	9080.2 [c)]	
			30	Day 1	Male	3[a)]	1141.8		236192 [b)]	
					Female	3[a)]	975.8		215607 [b)]	
				Day 29	Male	3[a)]	617.4	76	14829 [c)]	
					Female	3[a)]	637.8	22	15314 [c)]	
			100	Day 1	Male	3[a)]	4863.9		920323 [b)]	
					Female	3[a)]	4604.4		934129 [b)]	
				Day 29	Male	3[a)]	1983.7	40	47667 [c)]	
					Female	3[a)]	1995.3	81	47932 [c)]	
Rabbit	Intravenous (bolus)	23 days (once daily)	30	Gestation day 6	Female	3	1080.4	16.8	15581 [d)]	4.2.3.5.2-4
				Gestation day 28	Female	3	1347.2	18.0	26311 [d)]	
			100	Gestation day 6	Female	3	3932.8	14.6	55067 [d)]	
				Gestation day 28	Female	3	4086.1	14.9	74721 [d)]	
Monkey	Intravenous (0.5-hour continuous infusion)	26 weeks (once weekly)	10	Days 1 to 8	Male	6	250.9 ± 38.0	23.3 ± 6.9	3195 ± 245.8 [e)]	4.2.3.2-3
					Female	6	215.0 ± 45.5	23.5 ± 6.0	3258 ± 204.5 [e)]	
				Days 85 to 92	Male	5[f)]	206.6 ± 31.6	32.1 ± 9.1	3336 ± 475 [e)]	
					Female	3[f)]	148.2 ± 106.3	32.9, 40.0 [g)]	3363 ± 618.3 [e)]	
				Days 176 to 183	Male	5[f)]	188.4 ± 12.2	31.7 ± 0.7	4162 ± 575.3 [e)]	
					Female	3[f)]	226.0 ± 34.4	33.1 ± 4.1	5081 ± 305.1 [e)]	
			30	Days 1 to 8	Male	6	844.9 ± 81.4	29.3 ± 2.4	9584 ± 896.4 [e)]	
					Female	6	719.9 ± 119.4	30.0 ± 3.5	8424 ± 164.4 [e)]	
				Days 85 to 92	Male	6	707.0 ± 283.6	25.6 ± 8.6	10212 ± 885.7 [e)]	
					Female	6	696.3 ± 74.3	24.7 ± 8.4	8875 ± 1525 [e)]	
				Days 176 to 183	Male	5[f)]	835.5 ± 271.8	25.5 ± 7.1	11938 ± 2230 [e)]	
					Female	5[f)]	717.9 ± 12.1	30.6 ± 3.3	8657 ± 3467 [e)]	
			100	Days 1 to 8	Male	6	2523 ± 789.7	25.2 ± 1.9	30344 ± 2763 [e)]	
					Female	6	2221 ± 362.6	25.4 ± 1.3	30532 ± 643.8 [e)]	
				Days 85 to 92	Male	6	2653 ± 414.3	23.4 ± 6.2	44637 ± 26504 [e)]	
					Female	6	2563 ± 333.5	25.2 ± 2.6	44197 ± 11307 [e)]	
				Days 176 to 183	Male	6	2663 ± 465.3	23.9 ± 6.4	28262 ± 8105 [e)]	
					Female	6	2454 ± 323.2	25.3 ± 1.9	24678 ± 2645 [e)]	

Mean or mean ± SD
a) 3 of all 9 animals/timepoint, b) $AUC_{0\text{-t last}}$, c) AUC_t, d) $AUC_{0\text{-inf}}$, e) $AUC_{0\text{-168 h}}$, f) Animals that were less exposed to efgartigimod alfa due to the expression of ADAs were excluded. g) Individual values from 2 animals

4.2 Distribution

Efgartigimod alfa, a biotechnology product with an Fc region, is expected to be transferred to the placenta.

4.3 Excretion

In the 26-week repeated dose toxicity study in female monkeys, efgartigimod alfa 10, 30, or 100 mg/kg was intravenously infused over 0.5 hours once weekly, and 3-hour urine samples were collected on Days 1, 85, and 183 to determine urinary efgartigimod alfa concentrations. The results showed that efgartigimod alfa was excreted into urine (CTD 4.2.2.5-1, CTD 4.2.3.2-3).

Efgartigimod alfa, a biotechnology product with an Fc region, is expected to be transferred to human milk, as with endogenous IgG.

4.R Outline of the review conducted by PMDA

The non-clinical pharmacokinetic study results submitted did not indicate any particular problems.

5. Toxicity and Outline of the Review Conducted by PMDA

As toxicological data for efgartigimod alfa, the applicant submitted the results from a single dose toxicity study, repeated dose toxicity studies, reproductive and development toxicity studies, and a local tolerance study.

5.1 Single-dose toxicity

The acute toxicity of efgartigimod alfa was evaluated in an extended single intravenous dose toxicity study in cynomolgus monkeys (Table 10). No efgartigimod alfa-attributable deaths or systemic toxicities occurred, and the approximate lethal dose of intravenous efgartigimod alfa was 100 mg/kg.

Table 10. Summary of extended single dose toxicity study results

Test system	Route of administration	Dose (mg/kg)	Major findings	Approximate lethal dose (mg/kg)	Attached CTD
Male and female cynomolgus monkeys	Intravenous (2-hour continuous infusion)	0,[a] 10, 30, 50, 100	≥10: Infusion procedure-related hematoma/hemorrhage;[b] decrease in blood γ-globulin/globulin/IgG concentration; increase in blood A/G ratio ≥50: Acute inflammation/necrosis in the subcutis[c] Reversible	>100	4.2.3.1-1

a) Vehicle: physiological saline, b) Findings observed also in the control group
c) The applicant explained that endotoxins that were found in the batch used in the study might have contributed to the findings at the administration sites in the 50 mg/kg and 100 mg/kg groups (namely, reversible acute inflammation/necrosis in the subcutis).

5.2 Repeated-dose toxicity

A 4-week repeated intravenous dose toxicity study in rats, and 4- and 26-week repeated intravenous dose toxicity studies in cynomolgus monkeys were conducted [Table 11]. The major findings were a decrease in blood IgG concentration attributable to the pharmacology of efgartigimod alfa and related changes. No decreases in albumin or other immunoglobulins (IgM and IgA) were found. Lymphocyte phenotyping revealed no changes attributable to efgartigimod alfa in NK cells, T-helper cells, activated T-helper cells, cytotoxic T-cells, activated cytotoxic T-cells, immature T-cells, or B-cells.

In the 4-week repeated intravenous dose toxicity study in rats, the exposure ($AUC_{0\text{-}48h}$) to efgartigimod alfa at the no observed adverse effect level (NOAEL) (30 mg/kg) was 15,060 μg·h/mL. In the 26-week repeated intravenous dose toxicity study in cynomolgus monkeys, the exposure ($AUC_{0\text{-}168h}$) at the NOAEL (100 mg/kg) was 44,417 μg·h/mL. These exposure levels were approximately 5.9-fold and 5.0-fold, respectively, the human exposure ($AUC_{0\text{-}168h}$, 8879 μg·h/mL)[18] obtained at the clinical dose (10 mg/kg).

[18] The mean $AUC_{0\text{-}168h}$ value estimated in Japanese patients with gMG enrolled in the global phase III study (STD 5.3.5.1-2, Study 1704)

Table 11. Summary of repeated dose toxicity study results

Test system	Route of administration	Treatment duration	Dose (mg/kg)	Major findings	NOAEL (mg/kg/week)	Attached CTD
Male and female rats (Sprague-Dawley)	Intravenous (bolus)	4 weeks (every 2 days) + 4-week recovery	0,[a)] 10, 30, 100	≥10: A decrease in blood globulin/γ-globulin/IgG concentration, and an increase in blood albumin/A/G ratio/total protein/calcium 100: Kupffer cell hypertrophy/hyperplasia Reversible	30	4.2.3.2-1
Male and female cynomolgus monkeys	Intravenous (2-hour continuous infusion)	4 weeks (every 2 days) + 4-week recovery	0,[a)] 3, 30, 100	≥3: An increase in LUC count, a decrease in blood globulin/γ-globulin/IgG concentration, an increase in blood A/G ratio, hematoma/induration [b)] at the administration site (macroscopic), and hemorrhage/fibrosis/inflammatory necrosis/ perivasculitis[c)] at the administration site (subcutis/subcutis muscle) ≥30: Exacerbation of thrombus formation/recanalization 100: Cytoplasmic alteration/degeneration of diffuse hepatocytes and diffuse mixed inflammatory cell infiltrates Reversible or tended to reverse	30	4.2.3.2-2
Male and female cynomolgus monkeys	Intravenous (0.5-hour continuous infusion)	26 weeks (once weekly) + 8-week recovery	0,[a)] 10, 30, 100	≥10: Hematoma/hemorrhage[c)] at the administration site (macroscopic), a decrease in blood globulin/γ-globulin/IgG concentration, enlarged cervical lymph node, enlarged spleen, follicular cell hyperplasia, and hemorrhage/fibrosis/inflammatory necrosis/ perivasculitis[c)] at the administration site (subcutis/subcutis muscle) ≥30: Enlarged mandibular lymph node 100: Diarrhea attended with enteritis[d)]	100	4.2.3.2-3

a) Vehicle: Physiological saline
b) Hematoma was also observed in the control group. The efgartigimod alfa 30 mg/kg and 100 mg/kg groups had high incidences of hematoma/induration at the administration site, which the applicant however considered non-toxicities, because they are background lesions generally found after the administration of a biological preparation and were reversible.
c) The finding was also observed in the control group. The applicant considered that the findings at the administration site were not toxicities, because they are background lesions generally found after the administration of a biological preparation and were reversible. In the 100 mg group of the 4-week repeated intravenous dose study in cynomolgus monkeys, hemorrhage, fibrosis, inflammation necrosis, and perivasculitis at the administration site (subcutis/subcutis muscle) worsened. The applicant however considered that the worsening of these changes could have been attributable to excessive endotoxin, in light of endotoxin contained in the batch used in the study.
d) This was found in 1 female monkey, which also showed decreased motility, sunken eyelids, decreased body weight, dehydration, etc. There have been reports that cynomolgus monkeys had background diseases including enteritis, and bacterial or parasitic infection (*Toxicol Pathol.* 2010;38,642-657, *J Immunotoxicol.* 2010;7,79-92). Because the histopathological findings in the gastrointestinal tract of the female monkey resembled those cited in these reports (e.g., mucosal hemorrhage, hyperplasia of mucosal cells, and mucosal inflammation with mucosal erosion), and because the incidences of the findings were within the range of the laboratory historical data (0% to 25%), the applicant considered that the findings were not toxicities.

5.3 Genotoxicity

Because efgartigimod alfa, an IgG1 antibody fragment, is unlikely to directly interact with DNA or other chromosomal materials, no genotoxicity studies were conducted according to the "Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (PFSB/ELD Notification No. 0323-1 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour, and Welfare dated March 23, 2014)."

5.4 Carcinogenicity

Efgartigimod alfa is an FcRn-directed human IgG1 antibody fragment with modified amino acid residues. The repeated dose toxicity studies revealed neither changes such as preneoplastic or proliferative lesions nor effects on cytotoxic-T-cells ($CD8^+$ T cells), NK cells, or other immune cells [see Section 5.2]. Thus no carcinogenicity studies were conducted according to the "Preclinical Safety Evaluation of Biotechnology-Derived

Pharmaceuticals (PFSB/ELD Notification No. 0323-1 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour, and Welfare dated March 23, 2014)."

5.5 Reproductive and developmental toxicity

A fertility and early embryonic development study in rats, embryo-fetal development studies in rats and rabbits, and a study for effects on pre- and postnatal development, including maternal function in rats were conducted [Table 12]. None of the studies showed toxic effects of efgartigimod alfa.

In the embryo-fetal development studies in rats and rabbits, the exposures ($AUC_{0\text{-}23h}$) to efgartigimod alfa at the NOAELs (100 mg/kg/day in both rats and rabbits) were 6,456 μg·h/mL in rats and 49,443 μg·h/mL in rabbits. These exposures were approximately 5.1-fold and 39.0-fold, respectively, higher than the human exposure ($AUC_{0\text{-}168h}$, 8,879 μg/h/mL)[18] achieved at the clinical dose (10 mg/kg).

Table 12. Summary of reproductive and developmental study results

Type of study	Test system	Route of administration	Treatment duration	Dose (mg/kg)	Major findings	NOAEL (mg/kg/day)	Attached CTD
Fertility and early embryonic development	Male and female rats (Sprague Dawley)	Intravenous	Males: 42 or 43 days, beginning from 4 weeks premating (once daily) Females: 15 days premating to gestation day 7 (once daily)	0,[a] 30, 100	No toxic changes[b]	Male and female fertility: 100	4.2.3.5.1-1
Embryo-fetal development	Female rats (Sprague-Dawley)	Intravenous	Gestation days 6 to 17 (once daily)	0,[a] 30, 100	No toxic changes	Dams: 100 Embryo-fetal development: 100	4.2.3.5.2-2
	Female rabbits (NZW)	Intravenous	Gestation days 6 to 28 (once daily)	0,[a] 30, 100	No toxic changes[c]	Dams: 100 Embryo-fetal development: 100	4.2.3.5.2-4
Effects on pre- and postnatal development, including maternal function	Female rats (Sprague-Dawley)	Intravenous	Dams: Gestation day 6 to lactation day 21 (once daily)	0,[a] 30, 100	F0 dams: No toxic changes[d] F1 pups: No toxic changes[e]	Dams (general toxicity): 100 F1 pups (development): 100	4.2.3.5.3-1

a) Vehicle: Physiological saline
b) In the 30 mg/kg group, 1dam had high percentages of pre-and post-implantation embryonic loss. However, the applicant considered these were non-toxicity, because these findings were not seen in parent animals in the 100 mg/kg group.
c) A total of 2 dams in the 30 mg/kg group and 1 dam in the 100 mg/kg had miscarriages. However, the applicant considered these were non-toxicity, because of the incidence within the laboratory historical data (0% to 10%).
d) In the 100 mg/kg group, 1 F0 dam was found dead on gestation day 21. The applicant considered it a death related to incipient miscarriage and not toxicity, because it occurred in only 1 dam and attended with signs of miscarriage (vaginal hemorrhage and postimplantation resorption). Decreased gestation index was found in the F0 generation of the 30 mg/kg group. However, the applicant considered it non-toxicity, attributing it to 1 dam without viable pups in the group, and based on the gestation index in the study that was within the laboratory historical data (90% to 100%).
e) Attributing the decreased conception rate to infertility in 3 F1 dams in the 30 mg/kg group and 2 F1 dams in the 100 mg/kg group, and in light of the decreased gestation index due to 1 dam without viable pups in the F1 generation of 30 mg/kg group were within the laboratory historical ranges (conception rate, 80% to 100%; gestation index, 90% to 100%), the applicant considered these changes non-toxicity. The applicant also considered the ataxia, which was observed in the F1 generation of the 100 mg/kg group found only in 1 dam and its 4 litters but not in any litters of other dams, was non-toxicity.

5.6 Local tolerance

The local irritant effects of intravenous efgartigimod alfa were evaluated based on data including the results of the 26-week repeated dose toxicity study in cynomolgus monkeys (CTD 4.2.3.2-3), the fertility and early embryonic development study in rats (CTD 4.2.3.5.1-1), the embryo-fetal development study in rats (CTD 4.2.3.5.2-2), the study for effects on pre- and postnatal development, including maternal function in rats

(CTD 4.2.3.5.3-1), and the embryo-fetal development study in rabbits (CTD 4.2.3.5.2-4). The obtained data indicated no findings suggestive of local irritant effects of efgartigimod alfa as compared with the control.

In addition, a local tolerance study was conducted using a subcutaneous formulation of efgartigimod alfa, in which a single dose of efgartigimod alfa was administered intravenously, intraarterially, subcutaneously, perivenously, and intramuscularly [Table 13]. The study results provided no findings suggestive of local irritant effects of efgartigimod alfa, regardless of the administration route as compared with the control. Based on these results, the applicant explained that intravenous efgartigimod alfa was unlikely to have local irritant effects in humans.

Table 13. Summary of local tolerance study results

Test system	Test method	Results	CTD
Female rabbits (NZW)	A single dose of subcutaneous formulation containing efgartigimod alfa 150 mg/mL[a)] was administered intravenously (1 mL), intraarterially (1 mL), subcutaneously (1 mL), perivenously (0.25 mL), or intramuscularly (0.25 mL).	No findings suggestive of local irritant effects of efgartigimod alfa as compared with the control were observed, regardless of the administration route.	4.2.3.6-1

a) A subcutaneous formulation of efgartigimod alfa, containing 20 mmol/L histidine, 60 mmol/L sucrose, 100 mmol/L sodium chloride, and 0.04% polysorbate 20 (pH 6.0)

5.R Outline of the review conducted by PMDA

5.R.1 Effects of efgartigimod alfa on fetuses and offspring

PMDA asked to the applicant to explain the possibility that IgG in fetuses and offspring may be decreased as a result of exposure to efgartigimod alfa administered to their mothers during pregnancy or lactation, and the safety of efgartigimod alfa in fetuses and offspring.

The applicant's explanation:

- Efgartigimod alfa decreased IgG through its pharmacological action but did not inhibit T-cell or B-cell activities, and had no effects on FcRn-independent endogenous IgM and IgA, or albumin [see Section 5.2]. These findings suggest that efgartigimod alfa does not impair cell-mediated immunity, and thus is unlikely to affect the immune system. In addition, the reproduction toxicity studies in rats and rabbits showed neither impacts of efgartigimod alfa ≤100 mg/kg/day on the development or growth of fetuses and offspring, nor changes suggestive of infections [see Section 5.5]. These results suggest that efgartigimod alfa is unlikely to have serious adverse impacts on fetuses or offspring.
- The reproduction toxicity studies did not evaluate the exposure of efgartigimod alfa to fetuses, and the apparent fetal-to-maternal distribution ratio of efgartigimod alfa is thus unknown. However, antibodies including monoclonal antibodies, when bound to FcRn, are efficiently transported across the placenta at gestation week ≥30 in humans (*Birth Defects Res B Dev Reprod Toxicol.* 2009;86:328-44), and efgartigimod alfa is also expected to be transferred from mother to fetus. Also, decreased mother's IgG concentration by efgartigimod alfa's pharmacological action is presumed to reduce the placental transfer of IgG, leading to the impaired ability of the offspring to defend against infections.
- Although there is no information about the transfer of efgartigimod alfa to human milk or infants, IgG is generally known to transferred into human milk (*Birth Defects Res B Dev Reprod Toxicol.* 2009;86:328-44). Offspring are thus likely to be exposed to efgartigimod alfa through a transfer to milk.

- Accordingly, the package insert should provide cautionary notes including the following information.
  - In pregnant women, efgartigimod alfa, which crosses the placenta and decreases the placental transfer of IgG, is likely to decrease IgG and increase the risk of adverse events such as infections in fetuses and offspring. Therefore, pregnant women should receive efgartigimod alfa only if the potential benefits outweigh the risks. Furthermore, caution should be used for the offspring of patients receiving efgartigimod alfa during pregnancy, because of possible increased risk of infections after immunization with live or attenuated vaccines.
  - Despite the lack of data on the transfer of efgartigimod alfa into human milk, IgG has generally been reported to be transferred into human milk. Thus, efgartigimod alfa administered in lactating women may cause the offspring to be exposed to efgartigimod alfa through human milk. Therefore, the continuation or discontinuation of breastfeeding must be considered in light of the benefits of efgartigimod alfa treatment and breastfeeding.

PMDA accepted the applicant's explanations that the exposure of pregnant women to efgartigimod alfa may decrease IgG, thereby increasing the risk of adverse events such as infections in their fetuses and offspring, and that efgartigimod alfa administered to lactating women may be transferred into milk and may cause the offspring to be exposed to efgartigimod alfa. PMDA concluded that there were no major problems with the proposed cautionary notes to be given in the package insert.

5.R.2 Carcinogenicity

The applicant's explanation:

In view of the submitted toxicity study results and the following information from the published literature, efgartigimod alfa has a low risk of malignant tumors.

- The repeated dose toxicity studies of efgartigimod alfa detected no changes such as preneoplastic or proliferative lesions [see Section 5.2].
- In FcRn-knockout mice, no increase in the spontaneous development of malignant neoplasms was suggested (*J Immunol.* 2003;170:3528-33).
- FcRn knockout mice that were chronically exposed to azoxymethane, a chemical carcinogen, were highly susceptible to the development of colorectal malignancies as compared with wild-type mice. This particularly suggests an association of the immune induction mediated by CD8+ T-cells with the development of colorectal malignancies (*Immunity.* 2013;39:1095-107). In FcRn knockout mice transplanted with tumor cells for a lung metastasis experiment, the number of pulmonary nodules increased as compared with wild-type mice, suggesting that tumor development is likely associated with the maturation of NK cells that were already present in the FcRn knockout mice (*Front immunol.* 2018;9:2259). In contrast, the repeated dose toxicity studies showed no effects of efgartigimod alfa on CD8+ T-cells or NK cells, etc. Accordingly, efgartigimod alfa is unlikely to affect the cancer immune surveillance by CD8+ T-cells or NK cells.

Efgartigimod alfa, with its action to decrease serum IgG concentration selectively and transiently, may impair

the immune response to malignant tumors. Generally, immunosuppression is known to be a potential risk factor for cancer development in humans (*Reg Toxicol Pharmacol.* 2016;75:72-80, *Int J Toxicol.* 2010;29:435-66). PMDA asked the applicant to explain the occurrence of malignant tumors in the clinical studies of efgartigimod alfa.

The applicant's explanation:

- In a global phase III study (CTD 5.3.5.1-2, Study 1704), patients with a history of malignant tumors were excluded, because the selective and transient decrease in serum IgG concentration during treatment with efgartigimod alfa could impair the immune response to malignant tumors and induce the recurrence of the malignant tumors, which might have complicated the interpretation of the study results.
- Malignant tumor-related adverse events[19)] were reported in 1 patient in the placebo group (basal cell carcinoma) and 1 patient in the efgartigimod alfa group (rectal adenocarcinoma) in Study 1704. Rectal adenocarcinoma was a serious adverse event leading to study drug discontinuation, but its causal relationship to the study drug was ruled out. In a global long-term extension study (CTD 5.3.5.2-2, Study 1705), 10 malignant tumor-related adverse events were reported in 7 patients (prostate cancer/adenocarcinoma of colon, neoplasm malignant/squamous cell carcinoma/lung neoplasm malignant, pancreatic carcinoma, vulval cancer, squamous cell carcinoma, oropharyngeal squamous cell carcinoma, and basosquamous carcinoma in 1 patient each). Of these, 4 events in 5 patients (prostate cancer/adenocarcinoma of colon, lung neoplasm malignant, pancreatic carcinoma, and vulval cancer in 1 patient each) were serious, and 2 events in 2 patients led to study drug discontinuation (adenocarcinoma of colon and lung neoplasm malignant in 1 patient each), for all which a causal relationship to the study drug was ruled out.
- These results suggest that the risk of malignant tumors associated with the use of efgartigimod alfa is unlikely to become a clinically relevant problem. Therefore, no particular cautionary advice will be necessary in the package insert.

PMDA's view:

- The toxicity study results did not provide direct evidence of efgartigimod alfa's carcinogenicity. In view of this, and the occurrence of malignant tumor-related adverse events in the clinical studies taken into account, a risk of malignant tumors associated with the use of efgartigimod alfa has not been suggested. Thus, the applicant's explanation about the unnecessity of cautionary advice on the development of malignant tumors in the package insert is acceptable.
- However, efgartigimod alfa acts to selectively and transiently decrease serum IgG concentration and thus may impair the immune response to malignant tumors. Immunosuppression is generally known to be associated with an increased cancer risk in humans, and therefore the risk of malignant tumors associated with the impaired immune response due to decreased IgG concentrations by efgartigimod alfa cannot be completely denied. The clinical studies of efgartigimod alfa excluded patients with a history of malignant tumors, and risks of efgartigimod alfa in patients with malignant tumors remain unknown. In light of the

19) Events coded under the MedDRA SOC "Neoplasms benign, malignant and unspecified (incl cysts and polyps)"

limited number of patients enrolled in the studies, information about malignant tumor-related events should be further collected in the post-marketing setting.

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

Efgartigimod alfa is an intravenous injection preparation. Therefore, no studies were conducted on bioavailability or bioequivalence. Serum efgartigimod alfa concentrations were measured using ELISA with a lower limit of quantification of 300 ng/mL, and urine efgartigimod alfa concentrations were measured using ELISA with a lower limit of quantification of 50.0 ng/mL. Anti-efgartigimod alfa-binding antibodies were quantified using a bridging ELISA with a lower limit of quantification of 0.295 μg/mL or an ACE bridging ELISA with a lower limit of quantification of 506 μg/mL. Anti-efgartigimod alfa neutralizing antibodies were detected using an electrochemiluminescence immunoassay with a detection limit of 0.967 μg/mL. The drug product formulations[20)] used in the clinical studies[21)] were the early clinical study formulation and the late clinical study formulation, both of which were drug products in vials.

6.2 Clinical pharmacology

The applicant submitted evaluation data, in the form of results from a foreign phase I study in non-Japanese healthy adults (CTD 5.3.3.1-1, Study 1501), a foreign phase II study in non-Japanese patients with gMG (CTD 5.3.5.1-1, Study 1602), a global phase III study in Japanese and non-Japanese patients with gMG (CTD 5.3.5.1-2, Study 1704), and a global long-term extension study (CTD 5.3.5.2-2, Study 1705). The applicant also summited the results of a foreign phase I study in non-Japanese healthy adults (Reference CTD 5.3.3.1-2, Study 1702) and the results of population pharmacokinetic analyses (Reference CTD 5.3.3.5-1, Reference CTD 5.3.3.5-2) as reference data. Major study results are described in the following subsections.

6.2.1 Studies in healthy adults

Efgartigimod alfa or placebo was intravenously administered to non-Japanese healthy adults (37 subjects evaluable for pharmacokinetics) according to the regimens presented in Table 14. Tables 15 and 16 show the pharmacokinetic parameters of efgartigimod alfa, while Table 17 shows the percent changes from baseline in total IgG concentration (CTD 5.3.3.1-1, Study 1501).

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20) The early clinical study formulation was a drug product that was prepared using a drug substance prepared from a cell line different from that for the to-be-marketed formulation or the late clinical study formulation, and was demonstrated to be comparable to the post-change drug product formulations. The late clinical study formulation was a drug product that differed from the to-be-marketed formulation in terms of manufacturing scale, etc., and was demonstrated to be comparable to the to-be-marketed formulation.

21) The early clinical study formulation was used in Studies 1501 and 1602, while the late clinical study formulation was used in Studies 1702, 1704, and 1705.

Table 14. Dosage regimens for efgartigimod alfa in Study 1501

	Cohort	Dosage regimen
Single-ascending-dose part[a)]	1	A single intravenous dose of efgartigimod alfa 0.2 mg/kg or placebo (2-hour infusion)
	2	A single intravenous dose of efgartigimod alfa 2 mg/kg or placebo (2-hour infusion)
	3	A single intravenous dose of efgartigimod alfa 10 mg/kg or placebo (2-hour infusion)
	4	A single intravenous dose of efgartigimod alfa 25 mg/kg or placebo (2-hour infusion)
	5	A single intravenous dose of efgartigimod alfa 50 mg/kg or placebo (2-hour infusion)
Multiple-ascending-dose part[b)]	7	A total of 6 intravenous doses of efgartigimod alfa 10 mg/kg or placebo administered every 4 days (2-hour infusion)
	8	A total of 4 intravenous doses of efgartigimod alfa 25 mg/kg or placebo administered every 7 days (2-hour infusion)
	9	A total of 4 intravenous doses of efgartigimod alfa 10 mg/kg or placebo administered every 7 days (2-hour infusion)
	10	A total of 4 intravenous doses of efgartigimod alfa 25 mg/kg or placebo administered every 7 days (2-hour infusion)

a) The optional Cohort 6 was planned in the single-ascending-dose part but not implemented.
b) The multiple-ascending-dose part was originally planned to be comprised of only Cohorts 7 and 8. However, based on the results from these cohorts, a new cohort receiving efgartigimod alfa 10 mg/kg every 7 days or 25 mg/kg every 4 days was added as Cohort 9 (Protocol version 3). Later, 1 patient in Cohort 8 had a serious adverse event, which led to the discontinuation of the cohort. In response, the dosage regimen in Cohort 9 was fixed as efgartigimod alfa 10 mg/kg every 7 days, and Cohort 10 was added with the same dosage regimen as Cohort 8 (Protocol version 4).

Table 15. Pharmacokinetic parameters of efgartigimod alfa following a single intravenous dose in non-Japanese healthy adults (Study 1501)

Cohort	Dose (mg/kg)	N	C_{max} (μg/mL)	AUC_{0-t} (μg·h/mL)	$t_{1/2}$ (h)	CL (L/h)	Vz (L)
1	0.2	4	1.81 ± 0.285	103 ± 126	140 ± 109 [a)]	NC	NC
2	2.0	4	34.8 ± 5.13	936 ± 54.0	104 ± 7.88	0.14 ± 0.02	21.4 ± 3.33
3	10	4	209 ± 27.9	6770 ± 1520	85.1 ± 7.50	0.12 ± 0.03	14.8 ± 2.03
4	25	4	436 ± 47.4	12763 ± 2087	89.7 ± 2.33	0.15 ± 0.02	19.8 ± 2.28
5	50	4	1175 ± 493	23340 ± 3013	91.3 ± 4.84	0.16 ± 0.02	21.4 ± 2.29

Mean ± SD; NC, not calculated
a) N = 3

Table 16. Pharmacokinetic parameters of efgartigimod alfa following multiple intravenous doses in non-Japanese healthy adults (Study 1501)

Cohort	Dosage regimen	Timepoint	N	C_{max} (μg/mL)	C_{trough} (μg/mL)	AUC_t (μg·h/mL)
7	10 mg/kg (every 4 days)	First dose	5	161 ± 38.2	15.3 ± 3.9	4206 ± 496
		Fourth dose	5	202 ± 21.2	22.0 ± 4.3	5211 ± 309
		Sixth dose	5	192 ± 20.9	21.4 ± 3.8	4842 ± 714
9	10 mg/kg (every 7 days)	First dose	6	195 ± 30.7	8.0 ± 1.1	5392 ± 619
		Third dose	6	237 ± 40.5	10.2 ± 2.1	6024 ± 543
		Fourth dose	6	204 ± 22.2	ND	5612 ± 646
10	25 mg/kg (every 7 days)	First dose	6	535 ± 136	16.1 ± 5.4	12458 ± 3114
		Third dose	6	407 ± 73.0	18.9 ± 4.6	10061 ± 1977
		Fourth dose	6	485 ± 136	ND	11152 ± 1877

Mean ± SD; ND, not determined

Table 17. Percent changes from baseline in total IgG concentration following a single intravenous dose or multiple intravenous doses of efgartigimod alfa in non-Japanese healthy adults (Study 1501)

Single-ascending-dose part

Cohort	2 hours postdose	24 hours postdose	48 hours postdose	96 hours postdose	144 hours postdose	336 hours postdose	504 hours postdose	672 hours postdose
1 [a)]	-4.60 ± 4.47	3.01 ± 10.8	-1.41 ± 9.27	-4.48 ± 9.01	-2.66 ± 4.94	-4.98 ± 10.8	-3.07 ± 12.6	0.386 ± 11.0
	4	4	4	4	4	3	4	4
2 [b)]	-4.46 ± 12.7	8.65 ± 11.9	-4.31 ± 20.1	-17.9 ± 7.53	-11.8 ± 18.4	-22.7 ± 12.1	-8.89 ± 19.5	-6.95 ± 15.6
	4	4	4	4	4	4	4	4
3 [c)]	1.74 ± 44.9	-8.62 ± 8.34	-16.3 ± 3.37	-28.5 ± 6.12	-43.1 ± 7.81	-49.1 ± 11.1	-51.8 ± 10.2	-46.7 ± 9.69
	4	4	4	4	4	4	4	4
4 [d)]	-1.06 ± 15.4	-9.58 ± 11.9	-19.9 ± 7.25	-41.5 ± 3.52	-59.8 ± 5.64	-56.5 ± 13.6	-57.9 ± 7.18	-46.8 ± 12.6
	4	4	4	4	4	4	4	4
5 [e)]	0.839 ± 4.74	-10.9 ± 3.62	-19.0 ± 3.58	-38.1 ± 1.90	-43.5 ± 4.50	-53.1 ± 7.92	-42.8 ± 8.81	-33.5 ± 13.5
	4	4	4	4	4	4	4	4

Multiple-ascending-dose part

Cohort	First dose	Second dose		Third dose		Fourth dose[f)]			
	2 hours postdose	0 hours postdose	120 hours postdose[g)]	0 hours postdose	120 hours postdose[g)]	0 hours postdose	120 hours postdose[g)]	672 hours postdose	1344 hours postdose
7 [h)]	-1.29 ± 4.92	-33.9 ± 13.3	-52.2 ± 14.7	-56.6 ± 15.9	-63.5 ± 14.0	-76.1 ± 5.89	-75.9 ± 5.28	-24.0 ± 15.8	1.47 ± 15.9
	5	5	5	5	5	5	5	5	5
9 [i)]	-7.50 ± 6.21	-42.6 ± 9.84	-48.0 ± 16.1	-48.5 ± 13.1	-62.3 ± 9.29	-61.1 ± 9.42	-67.8 ± 8.99	-31.6 ± 11.7	ND
	6	6	6	6	6	6	6	6	ND
10 [j)]	-5.18 ± 8.64	-48.9 ± 9.89	-64.8 ± 4.80	-66.5 ± 4.12	-67.3 ± 3.66	-67.3 ± 4.75	-69.4 ± 3.34	-40.3 ± 13.6	-7.03 ± 25.0
	6	6	6	6	6	5	6	6	6

Top, mean ± SD; bottom, N; ND, not determined
Cohort 1, 0.2 mg/kg; Cohort 2, 2 mg/kg; Cohort 3, 10 mg/kg; Cohort 4, 25 mg/kg; Cohort 5, 50 mg/kg; Cohort 7, 10 mg/kg every 4 days; Cohort 9, 10 mg/kg every 7 days; Cohort 10, 25 mg/kg every 7 days
a) Baseline total IgG concentration (mean ± SD), 6013 ± 1419 μg/mL; b) Baseline total IgG concentration, 8903 ± 3896 μg/mL;
c) Baseline total IgG concentration, 10,910 ± 2837 μg/mL; d) Baseline total IgG concentration, 7043 ± 3129 μg/mL;
e) Baseline total IgG concentration, 6663 ± 2165 μg/mL; f) Sixth dose in Cohort 7; g) 72 hours postdose in Cohort 7;
h) Baseline total IgG concentration, 9094 ± 2227 μg/mL; i) Baseline total IgG concentration, 8705 ± 2481 μg/mL
j) Baseline total IgG concentration, 10,792 ± 6233 μg/mL

Efgartigimod alfa 10 mg/kg was administered to non-Japanese healthy adults (15 subjects evaluable for pharmacokinetics) as a single intravenous dose (2-hour infusion) or multiple intravenous doses once weekly for 4 times (1-hour infusion). Table 18 shows the pharmacokinetic parameters of efgartigimod alfa, and Table 19 the percent changes from baseline in total IgG concentration (Reference CTD 5.3.3.1-2, Study 1702[22)]).

Table 18. Pharmacokinetic parameters of efgartigimod alfa following a single intravenous dose or multiple once-weekly intravenous doses of 10 mg/kg in non-Japanese healthy adults (Study 1702)

	Timepoint	N	C_{max} (μg/mL)	t_{max} (h)	AUC_{0-t} (μg·h/mL)	$t_{1/2}$ (h)	CL (L/h)	Vz (L)
Single dose	Day 1	8	206 ± 55.5	2.0 [2.0, 4.0]	6210 ± 1050	78.7 ± 16.9	0.13 ± 0.02	14.5 ± 2.6
Multiple doses	Day 22	7	188 ± 30.2	2.0 [1.0, 2.0]	7550 ± 1450	82.1 ± 7.6	0.12 ± 0.02	14.2 ± 2.6

Mean ± SD, or median for t_{max} [range]

22) Study 1702 is a foreign phase I study in non-Japanese healthy adults (39 subjects evaluable for pharmacokinetics), consisting of 4 cohorts. In Cohort A, a single intravenous dose of efgartigimod alfa 10 mg/kg was administered (2-hour infusion). In Cohort B, a single dose of subcutaneous formulation of efgartigimod alfa 10 mg/kg was administered in the abdomen (2-hour infusion). In Cohort C, efgartigimod alfa 20 mg/kg was intravenously administered on Days 1 and 4 (2-hour infusion), and a subcutaneous formulation of efgartigimod alfa 300 mg was administered in the abdomen from Day 8 once weekly for 8 weeks. In Cohort D, intravenous efgartigimod alfa 10 mg/kg was administered on Days 1, 8, 15, and 22 (1-hour infusion). The pharmacokinetics and pharmacodynamics of efgartigimod alfa described in this review report are based on the intravenous doses, in light of the proposed dosage and administration.

Table 19. Percent changes from baseline in total IgG concentration following a single intravenous dose or multiple once-weekly intravenous doses of efgartigimod alfa 10 mg/kg in non-Japanese healthy adults (Study 1702)

Single dose[a)]						
Day 2	Day 4	Day 7	Day 15	Day 22	Day 29	Day 57/end of the study
-14.4 ± 9.9 (8)	-25.4 ± 10.2 (8)	-40.3 ± 8.3 (8)	-42.5 ± 9.7 (8)	-33.9 ± 8.1 (8)	-24.0 ± 11.5 (8)	-11.0 ± 10.9 (8)

Multiple doses[b)]					
Day 8[c)]	Day 15[d)]	Day 22[e)]	Day 28	Day 50	Day 78/end of the study
-46.3 ± 3.7 (8)	-62.7 ± 3.8 (7)	-66.3 ± 3.1 (7)	-68.4 ± 5.6 (7)	-33.7 ± 6.7 (7)	-5.11 ± 8.6 (7)

Mean ± SD (n)
a) Baseline total IgG concentration (mean ± SD), 11,511 ± 4275 μg/mL; b) Baseline total IgG concentration, 10,795 ± 2962 μg/mL
c) Second dose; d) Third dose; e) Fourth dose

6.2.2 Studies in patients with gMG

Efgartigimod alfa 10 mg/kg was administered to non-Japanese patients with gMG[23)] (12 patients evaluable for pharmacokinetics) as once-weekly intravenous doses for 4 times (2-hour infusion). Table 20 shows the pharmacokinetic parameters of efgartigimod alfa, and Table 21 the percent changes from baseline in total IgG concentration (Reference CTD 5.3.5.1-1, Study 1602).

Table 20. Pharmacokinetic parameters of efgartigimod alfa following once-weekly intravenous doses of 10 mg/kg in non-Japanese patients with gMG (Study 1602)

Timepoint	C_{max} (μg/mL)	C_{trough} (μg/mL)	$AUC_{0\text{-}168h}$ (μg·h/mL)	$t_{1/2}$ (h)
First dose	187.2 ± 58.0 (12)	NA	8930 ± 3127 (11)	
Second dose	176.8 ± 32.2 (11)	7.8 ± 2.9 (12)	9036 ± 2337 (11)	
Third dose	156.5 ± 33.2 (11)	11.1 ± 5.4 (11)	8557 ± 2558 (11)	
Fourth dose	167.6 ± 43.7 (11)	11.2 ± 5.2 (11)	8284 ± 2784 (10)	117.4 ± 18.8 (12)

Mean ± SD (n); NA, not assessable

Table 21. Percent changes from baseline in total IgG concentration following once-weekly intravenous doses of efgartigimod alfa 10 mg/kg in non-Japanese patients with gMG (Study 1602)

Day 8[a)]	Day 15[b)]	Day 22[c)]	Day 29	Day 78/end of the study
-42.1 ± 15.2 (12)	-60.9 ± 8.7 (12)	-70.0 ± 11.0 (12)	-69.9 ± 11.6 (12)	-20.4 ± 25.0 (12)

Mean ± SD (n)
Baseline total IgG concentration (mean ± SD), 10,591 ± 5077 μg/mL; a) Second dose; b) Third dose; c) Fourth dose

Japanese and non-Japanese patients with gMG (84 patients evaluable for pharmacokinetics) were treated in 3 cycles, in each of which intravenous efgartigimod alfa 10 mg/kg was administered once weekly for 4 times (1-hour infusion). Table 22 shows the pharmacokinetics of efgartigimod alfa during the 3 treatment cycles, while Table 23 shows the percent changes from baseline in total IgG concentration during the 3 treatment cycles (CTD 5.3.5.1-2, Study 1704).

23) All patients enrolled in the study tested positive for anti-AChR antibodies.

Table 22. Pharmacokinetic parameters of efgartigimod alfa following once-weekly intravenous doses of 10 mg/kg for 4 times in Japanese and non-Japanese patients with gMG (Study 1704)

	Timepoint	Japanese			Non-Japanese	
		C_{max} (μg/mL)	C_{trough} (μg/mL)	$AUC_{0\text{-}168h}$ [a] (μg·h/mL)	C_{max} (μg/mL)	C_{trough} (μg/mL)
Cycle 1	First dose	213 ± 20.1 (8)		7376 ± 1024 (8)	245 ± 243 (72)	
	Second dose	197 ± 85.5 (8)	11.2 ± 2.3 (8)	NC	239 ± 71.7 (73)	14.2 ± 29.8 (74)
	Third dose	235 ± 33.5 (8)	14.4 ± 4.7 (8)	NC	234 ± 79.6 (72)	12.7 ± 6.6 (72)
	Fourth dose	237 ± 43.3 (7)	13.4 ± 3.7 (8)	8879 ± 1667 (7)	254 ± 205 (73)	12.7 ± 6.5 (73)
Cycle 2	First dose	219 ± 45.8 (6)		8042 ± 787 (6)	221 ± 66.6 (56)	
	Second dose	231 ± 49.0 (6)	12.2 ± 4.8 (6)	NC	232 ± 59.8 (57)	10.2 ± 4.3 (57)
	Third dose	217 ± 46.0 (6)	10.8 ± 3.1 (6)	NC	244 ± 95.0 (55)	12.5 ± 6.6 (55)
	Fourth dose	184 ± 41.5 (6)	12.1 ± 7.0 (6)	6700 ± 1611 (6)	253 ± 198 (54)	12.9 ± 6.9 (54)
Cycle 3	First dose	ND		ND	226 ± 21.2 (7)	
	Second dose	ND	ND	ND	174 ± 113 (5)	36.4 ± 69.9 (6)
	Third dose	ND	ND	ND	145 ± 19.7 (5)	7.1 ± 2.9 (4)
	Fourth dose	ND	ND	ND	153 ± 24.5 (5)	7.5 ± 1.3 (5)

Mean + SD (n); NC, not calculated; ND, not determined

a) Only Japanese patients provided blood samples at 48 and 96 hours after the first and fourth doses, as well as immediately predose and immediately postdose to determine $AUC_{0\text{-}168h}$ values.

Table 23. Percent changes from baseline in total IgG concentration following once-weekly intravenous doses of efgartigimod alfa 10 mg/kg for 4 times in Japanese and non-Japanese patients with gMG (Study 1704)

	Efgartigimod alfa						Placebo					
	Week 1	Week 2	Week 4	Week 6	Week 8	Week 12	Week 1	Week 2	Week 4	Week 6	Week 8	Week 12
Anti-AChR antibody-positive[b]												
Cycle 1	-37.7 ± 1.3	-54.4 ± 1.2	-61.3 ± 0.9	-37.9 ± 1.4	-18.2 ± 1.8	-6.1 ± 2.8	0.8 ± 2.1	-0.9 ± 1.9	0.6 ± 2.7	4.7 ± 4.1	2.1 ± 2.3	-0.1 ± 5.5
	65	63	63	63	63	25	60	63	63	62	59	16
Cycle 2	-39.2 ± 1.8	-55.4 ± 1.2	-60.9 ± 1.3	-40.1 ± 1.8	-16.4 ± 2.5	0.3 ± 6.0	2.2 ± 3.8	1.3 ± 4.5	-2.3 ± 3.3	-0.1 ± 3.1	-0.3 ± 3.1	-4.2 ± 6.4
	50	50	46	47	45	7	42	43	42	41	41	7
Anti-AChR antibody-negative/anti-MuSK antibody-negative[b]												
Cycle 1	-45.2 ± 3.1	-61.5 ± 1.4	-67.3 ± 1.4	-47.7 ± 3.4	-25.6 ± 3.4	-6.0 ± 5.8	3.0 ± 3.9	-0.2 ± 3.4	0.3 ± 4.3	-4.1 ± 3.2	2.1 ± 3.3	5.6 ± 5.6
	16	15	14	15	15	9	16	16	16	16	16	6
Cycle 2	-48.9 ± 3.9	-62.7 ± 3.0	-64.2 ± 5.2	-51.5 ± 5.5	-29.6 ± 5.7	-27.5 ± 12.1	-2.5 ± 3.9	6.5 ± 5.7	6.2 ± 8.6	-2.8 ± 5.9	-6.4 ± 6.7	-14.7 ± 7.2
	10	10	10	8	10	3	12	12	13	13	12	3
Anti-AChR antibody-negative/anti-MuSK antibody-positive[b]												
Cycle 1	-40.3 ± 3.5	-49.8 ± 4.6	-56.8 ± 3.5	-32.7 ± 8.5	2.5 ± 14.7	-5.8 ± 5.4	-12.2 ± 7.0	-18.7 ± 6.4	-11.5 ± 9.5	-9.0 ± 7.0	-4.0 ± 4.1	-13.3, 21.8[a]
	3	3	3	3	3	3	3	3	3	3	3	2
Cycle 2	-47.5, -40.9[a]	-63.3, -38.6[a]	-69.4, -41.1[a]	-50.9[a]	-19.0, -13.1[a]	-28.6[a]	-17.9[a]	-22.6[a]	NC	-23.9[a]	-29.1[a]	-8.2[a]
	2	2	2	1	2	1	1	1	0	1	1	1

Top, mean ± SE; bottom, n; NC, not calculated

a) Individual values

b) Baseline total IgG concentrations (mean ± SE), 8345 ± 312 μg/mL in the efgartigimod alfa group and 7889 ± 281 μg/mL in the placebo group

6.2.3 Population pharmacokinetic/pharmacodynamic analyses (Reference CTD 5.3.3.5-1, Reference CTD 5.3.3.5-2)

Based on serum efgartigimod alfa concentration data (1397 time points, 84 patients) from the global phase III study in patients with gMG (CTD 5.3.5.1-2, Study 1704), the population pharmacokinetic model[24] (Reference CTD 5.3.3.5-1) was updated. The final model was described by a linear 3-compartment model, under the assumption that 2 peripheral compartments were included. Based on a covariate analysis,[25] body weight and

[24] A population pharmacokinetic model that was constructed based on serum efgartigimod alfa concentration data from a foreign phase I study in healthy adults (CTD 5.3.3.1-1, Study 1501) and a foreign phase II study in patients with gMG (CTD 5.3.5.1-1, Study 1602)

[25] The potential covariates evaluated included age, gender, race, ethnicity, body weight, body mass index (BMI), eGFR, albumin, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), ADA status, and concomitant gMG medications.

estimated glomerular filtration rate (eGFR) were incorporated as covariates for CL, and body weight as the covariate for V1.

In a simulation of the 4 doses of efgartigimod alfa 10 mg/kg administered once weekly, the $AUC_{0\text{-}168h}$ was estimated to be decreased by 20% in patients weighing 53 kg (5th percentile of body weight) and increased by 44% in patients weighing 129.8 kg (95th percentile of body weight) as compared with patients weighing 76.05 kg (median of body weight).[26)] In a similar simulation, the $AUC_{0\text{-}168h}$ was estimated to be increased by 72% in patients with an eGFR of 62.2 mL/min/1.73 m^2 (5th percentile of eGFR) and decreased by 21% in patients with an eGFR of 122.4 mL/min/1.73 m^2 (95th percentile of eGFR) as compared with patients with an eGFR of 100.27 mL/min/1.73 m^2 (median of eGFR).[27)]

A population pharmacokinetic/pharmacodynamic model was constructed using the established population pharmacokinetic model. The stimulation of IgG degradation rate by efgartigimod alfa was described by an indirect response model, with an EC_{50} of 41.4 μg/mL in terms of total IgG concentration.

6.R Outline of the review conducted by PMDA

6.R.1 Comparisons of pharmacokinetics and pharmacodynamics between Japanese and non-Japanese patients

The applicant's explanation about the differences in the pharmacokinetics and pharmacodynamics of efgartigimod alfa between Japanese and non-Japanese patients:

- Table 24 shows the pharmacokinetic parameters of efgartigimod alfa in Japanese and non-Japanese patients participated in the foreign phase II study targeting non-Japanese patients with gMG (CTD 5.3.5.1-1, Study 1602) or the global phase III study in Japanese and non-Japanese patients with gMG (CTD 5.3.5.1-2, Study 1704). The pharmacokinetic results were similar in Japanese and non-Japanese patients.

Table 24. Pharmacokinetic parameters of efgartigimod alfa following once-weekly intravenous doses of 10 mg/kg in Japanese and non-Japanese patients with gMG

Timepoint	Japanese[a)]			Non-Japanese[b)]		
	C_{max} (μg/mL)	C_{trough} (μg/mL)	$AUC_{0\text{-}168h}$ (μg·h/mL)	C_{max} (μg/mL)	C_{trough} (μg/mL)	$AUC_{0\text{-}168h}$ (μg·h/mL)
First dose	213 ± 20.1 (8)		7376 ± 1024 (8)	245 ± 243 (72)		8930 ± 3127 (11)
Fourth dose	237 ± 43.3 (7)	13.4 ± 3.7 (8)	8879 ± 1667 (7)	254 ± 205 (73)	12.7 ± 6.5 (73)	8284 ± 2784 (10)

Mean ± SD (n)
a) Data from Study 1704 (Cycle 1)
b) C_{max} and C_{trough} data from Study 1704 (Cycle 1), and $AUC_{0\text{-}168h}$ data from Study 1602

- In the population pharmacokinetic analysis using data from Study 1704 [see Section 6.2.3], ethnicity (Japanese vs. non-Japanese) was not selected as a covariate. The steady-state C_{trough} and $AUC_{0\text{-}168h}$ values (median [95% CI]) during Cycle 1 estimated using the final model were 12.3 [10.9, 13.7] μg/mL and 6706 [6383, 7029] μg·h/mL, respectively, in Japanese patients and 11.0 [9.9, 12.2] μg/mL and 6935 [6417, 7452] μg·h/mL, respectively, in non-Japanese patients. Thus, the 2 populations had similar exposure to

26) The eGFR was fixed at 100.27 mL/min/1.73 m^2 (median).
27) The body weight was fixed at 76.05 kg (median).

efgartigimod alfa.

- Table 25 presents the percent changes from baseline to Week 4 (1 week after the last dose of efgartigimod alfa) in the concentrations of total IgG and IgG subclasses in each cycle of Study 1704. There were no evident differences in the changes from baseline between Japanese and non-Japanese patients.

Table 25. Percent changes from baseline to Week 4 (1 week after the last dose of efgartigimod alfa) in the concentrations of total IgG and IgG subclasses following once-weekly intravenous doses of efgartigimod alfa 10 mg/kg in Japanese and non-Japanese patients with gMG (Study 1704, anti-AChR antibody-positive patients)

		Japanese		Non-Japanese	
Total IgG[a)]		Cycle 1	Cycle 2	Cycle 1	Cycle 2
		-61.5 ± 2.75 (6)	-64.5 ± 5.49 (5)	-61.3 ± 0.98 (57)	-60.5 ± 1.32 (41)
IgG subclasses	IgG1[b)]	-67.1 ± 2.50 (6)	-64.0, -66.0[f)] (2)	-67.6 ± 1.04 (56)	-62.0 ± 2.06 (41)
	IgG2[c)]	-61.4 ± 4.41 (6)	-64.7 ± 3.65 (5)	-59.4 ± 1.80 (57)	-60.0 ± 2.73 (42)
	IgG3[d)]	-55.8 ± 3.05 (6)	-64.3 ± 3.82 (5)	-64.0 ± 1.28 (57)	-61.0 ± 2.14 (42)
	IgG4[e)]	-41.9 ± 7.63 (6)	-51.4 ± 4.30 (5)	-53.1 ± 1.71 (57)	-43.8 ± 4.24 (42)

Mean ± SE (n)
a) Baseline total IgG concentrations (mean ± SE), 7903 ± 1129 μg/mL in Japanese patients and 8390 ± 326 μg/mL in non-Japanese patients
b) Baseline IgG1 concentrations, 6125 ± 937 μg//mL in Japanese patients and 7280 ± 272 μg/mL in non-Japanese patients
c) Baseline IgG2 concentrations, 4442 ± 611 μg/mL in Japanese patients and 4860 ± 234 μg/mL in non-Japanese patients
d) Baseline IgG3 concentrations, 246 ± 110 μg/mL in Japanese patients and 640 ± 38.3 μg/mL in non-Japanese patients
e) Baseline IgG4 concentrations, 244 ± 134 μg/mL in Japanese patients and 392 ± 47.4 μg/mL in non-Japanese patients
f) Individual values from 2 patients

- The above results indicated no particular differences in the pharmacokinetics or pharmacodynamics of efgartigimod alfa between Japanese and non-Japanese patients, with no evidence demonstrating that either the pharmacokinetics or pharmacodynamics of efgartigimod alfa was affected by ethnic factors.

PMDA accepted the applicant's explanation that there were no particular differences in the pharmacokinetics or pharmacodynamics between Japanese and non-Japanese patients.

6.R.2 Dosage and administration for efgartigimod alfa from a clinical pharmacological standpoint

The applicant's explanation about the dosage and administration for efgartigimod alfa from a clinical pharmacological standpoint:

- Table 17 shows the percent changes from baseline in total IgG concentration following a single intravenous dose of efgartigimod alfa 0.2 to 50 mg/kg in the phase I study in healthy subjects (CTD 5.3.3.1-1, Study 1501). Total IgG concentration decreased in a dose-dependent manner at doses of ≤10 mg/kg (Cohorts 1 to 3). When efgartigimod alfa 10 or 25 mg/kg were intravenously administered once weekly for 4 times (Cohorts 9 and 10), the decrease in total IgG concentration reached equilibrium by the last dose (fourth dose) and peaked approximately 1 week after the last dose, returning to baseline by approximately 8 weeks after the last dose [Figure 1].
- The maximum percent decrease in total IgG concentration after 4 intravenous doses of efgartigimod alfa 10 mg/kg did not clearly differ between dosing every 4 days (cohort 7) and dosing every 7 days (cohort 9) [Table 17 and Figure 1].

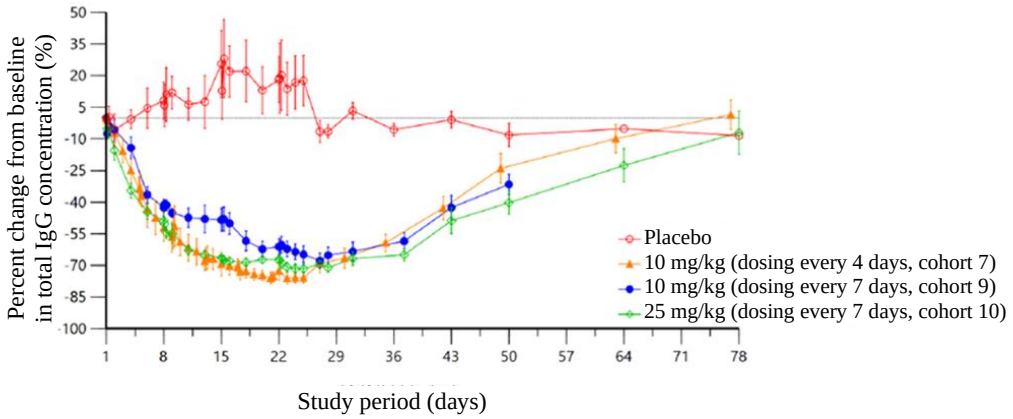

Figure 1. Percent changes from baseline in total IgG concentration following multiple intravenous doses of efgartigimod alfa in non-Japanese healthy adults (Study 1501, cohorts 7, 9, and 10)

- The autoantibodies predominantly found in patients with gMG were IgG1 (anti-AChR antibodies), IgG3 (anti-AChR antibodies), and IgG4 (anti-MuSK antibodies). Table 26 shows the percent changes from baseline in each IgG subclass following intravenous doses of efgartigimod alfa 10 mg/kg administered every 7 days for 4 times (cohort 9). Although the percent decrease in IgG4 tended to be smaller than those in other subclasses, efgartigimod alfa therapy was shown to decrease all IgG subclasses.

Table 26. Percent changes from baseline in IgG subclasses (Study 1501, cohort 9 [10 mg/kg every 7 days])

IgG subclasses	First dose	Second dose		Third dose		Fourth dose		
	2 hours postdose	0 hours postdose	120 hours postdose	0 hours postdose	120 hours postdose	0 hours postdose	120 hours postdose	672 hours postdose
IgG1 a)	-5.65 ± 3.26	-39.2 ± 11.0	-59.7 ± 8.95	-60.5 ± 7.16	-69.3 ± 6.28	-68.4 ± 7.56	-71.8 ± 6.28	-40.4 ± 9.10
	6	6	6	6	6	6	6	6
IgG2 b)	-3.68 ± 6.45	-26.0 ± 10.1	-43.3 ± 9.17	-45.3 ± 8.51	-54.7 ± 8.08	-57.2 ± 6.00	-62.0 ± 5.73	-45.9 ± 8.37
	6	6	6	6	6	6	6	6
IgG3 c)	-4.43 ± 7.04	-45.6 ± 12.6	-63.4 ± 9.88	-62.9 ± 8.48	-70.0 ± 7.34	-67.7 ± 7.95	-71.2 ± 7.30	-25.6 ± 13.8
	6	6	6	6	6	6	6	6
IgG4 d)	-3.84 ± 7.23	-26.1 ± 10.8	-44.6 ± 8.07	-44.7 ± 8.76	-54.5 ± 6.88	-54.1 ± 7.50	-56.7 ± 7.12	-22.9 ± 9.14
	6	6	6	6	6	6	6	6

Top, mean ± SD; bottom, n
a) Baseline IgG1 concentration (mean ± SD), 6790 ± 1836 μg/mL; b) Baseline IgG2 concentration, 5997 ± 1385 μg/mL; c) Baseline IgG3 concentration, 524 ± 163 μg/mL; d) Baseline IgG4 concentration, 548 ± 530 μg/mL

- The decrease in total IgG concentration was also observed in a foreign phase II study, in which efgartigimod alfa 10 mg/kg was intravenously administered once weekly for 4 times to non-Japanese patients with gMG (CTD 5.3.5.1-1, Study 1602), based on the results of Study 1501 [Table 21]. A population pharmacokinetic/pharmacodynamic model was established based on the data from Studies 1501 and 1602 (Reference CTD 5.3.3.5-1), and a simulation using the model[28] estimated the maximum percent decreases (median [5th percentile, 95th percentile]) from baseline in total IgG concentration following the administration of intravenous efgartigimod alfa 5, 10, and 20 mg/kg4 once weekly for 4 times. The results of estimation were 62 [49, 75]%, 71 [59, 78]%, and 77 [70, 81]%, respectively.
- When efgartigimod alfa 10 mg/kg were intravenously administered over 1 or 2 hours once weekly for 4 times in Study 1501 and a foreign phase I study in non-Japanese healthy adults (Reference CTD 5.3.3.1-2,

[28] The percent decreases in total IgG concentration following once-weekly doses of placebo or efgartigimod alfa 5, 10, and 20 mg/kg were estimated every 4 weeks in 60 patients for each treatment group.

Study 1702), the 1-hour infusion (Study 1501, Cohort 9) provided C_{max} and $AUC_{0\text{-}72h}$ values (mean ± SD) of 204 ± 22.2 μg/mL and 4168 ± 541 μg·h/mL, respectively, while the 2-hour infusion (Study 1702) provided values of 188 ± 30.2 μg/mL and 4430 ± 478 μg·h/mL, respectively. Thus, the C_{max} and $AUC_{0\text{-}72h}$ of efgartigimod alfa were similar after 1- and 2-hour infusion.

- Based on the above study results, intravenous infusion of efgartigimod alfa 10 mg/kg over 1 hour once weekly for 4 times was defined as the dosage regimen for the global phase III study in Japanese and non-Japanese patients with gMG (CTD 5.3.5.1-2, Study 1704).
- The percent changes from baseline in total IgG concentration following multiple intravenous doses in Study 1704 are shown in Table 23. The total IgG concentration was confirmed to be decreased by efgartigimod alfa 10 mg/kg intravenously infused over 1 hour once weekly for 4 times in a treatment cycle.

PMDA accepted the above applicant's explanation. The dosage regimen of efgartigimod alfa 10 mg/kg administered over 1 hour once weekly is considered appropriate from a clinical pharmacological standpoint. The appropriateness of the dosage regimen is further discussed in Section 7.R.6, with the efficacy and safety data from the clinical studies taken into consideration.

6.R.3 Use of efgartigimod alfa in patients with renal impairment

PMDA asked the applicant to explain the impact of renal impairment on the pharmacokinetics of efgartigimod alfa and the use of efgartigimod alfa in patients with renal impairment.

The applicant's explanation:

- Albumin, which has a molecular weight of 69 kDa, is filtered in glomeruli and actively reabsorbed by the proximal renal tubules (*Int J Nephrol.* 2012:48;1-9). Likewise, efgartigimod alfa has a molecular weight of approximately 54 kDa and is presumed to be partially filtered in glomeruli, and with its high affinity for human FcRn in both neutral and acidic pH conditions, actively reabsorbed by the proximal renal tubules.
- A clinical study investigating the impact of renal functions on the pharmacokinetics of idarucizumab, an antibody fragment with a molecular weight of 48 kDa, showed increased AUC by 28.4% in patients with mild renal impairment and by 83.5% in patients with moderate renal impairment as compared with healthy adults (*Clin Pharmacokinet.* 2017:56;41-54). In patients with severe digoxin poisoning or digitoxin poisoning treated with a digoxin-specific antibody Fab fragment with a molecular weight of 46 kDa, the decrease in the clearance of the Fab fragment was linearly proportional to decreasing creatinine clearance and increasing age (*Br J Clin Pharmacol.* 1997:44;135-8).
- In the foreign phase I study in healthy subjects (CTD 5.3.3.1-1, Study 1501), a single intravenous dose of efgartigimod alfa 10 mg/kg was excreted into urine at a urinary excretion rate of <0.1%. In Study 1501, healthy subjects received intravenous efgartigimod alfa 10 or 25 mg/kg once-weekly for 4 times and were found to be increasingly exposed to efgartigimod alfa in a generally dose-proportional manner. There were no problems with the safety or tolerability of efgartigimod alfa at doses of ≤25 mg/kg [see Section 7.1].
- Table 27 shows the incidences of adverse events in patients with normal renal function, mild renal impairment, or moderate renal impairment in the global phase III study (CTD 5.3.5.1-2, Study 1704). The

incidences of adverse events, in terms of respective events as well, were not substantially affected by the severity of renal impairment.

Table 27. Incidences of adverse events by the severity of renal impairment (Study 1704)

	Normal renal function (N = 103)	Mild renal impairment (N = 53)	Moderate renal impairment (N = 6)
All adverse events	82/103 (79.6)	44/53 (83.0)	4/6 (66.7)
Serious adverse events	11/103 (10.7)	9/53 (17.0)	1/6 (16.7)

n/N (%)

- As a result of the population pharmacokinetic analysis [see Section 6.2.3], eGFR was selected as a covariate for CL. Simulations based on the established population pharmacokinetic analysis model indicated that the $AUC_{0\text{-}168h}$ of a total of 4 doses of efgartigimod alfa 10 mg/kg administered once weekly for would be high by 72% in patients with an eGFR of 62.2 mL/min/1.73 m^2 (5th percentile of eGFR) as compared with patients with an eGFR of 100 mL/min/1.73 m^2 (median of eGFR). Similarly, simulations indicated that the $AUC_{0\text{-}168h}$ would be high by 28% in patients with mild renal impairment (eGFR, ≥60 mL/min/1.73 m^2 to <90 mL/min/1.73 m^2) as compared with patients with normal renal function (eGFR, ≥90 mL/min/1.73 m^2).
- Due to the lack of data, it remains unclear whether the exposure to efgartigimod alfa 10 mg/kg administered in patients with severe renal impairment will fall within the range of the exposure levels of efgartigimod alfa 25 mg/kg shown in Study 1501. However, the results of Study 1501 indicate minimal contribution of renal excretion to the clearance of efgartigimod alfa from the body. In addition, taking account of the magnitude of increases in exposure to efgartigimod alfa in patients with renal impairment, as estimated by the population pharmacokinetic analysis (approximately 1.3-fold higher in patients with mild renal impairment and approximately 1.7-fold higher in patients with an eGFR of 62.2 mL/min/1.73 m^2 [5th percentile of eGFR]) [see Section 6.2.3], exposures in patients with severe renal impairment are presumed to be within the range that was demonstrated to be safe in the clinical studies. Thus, at present, there is no information suggestive of the possibility that the use of efgartigimod alfa may pose safety problems in patients with severe renal impairment.
- These findings indicate that efgartigimod alfa, like other fragment preparations or albumin, is partially excreted through the kidneys, and the population pharmacokinetic analysis predicted that exposure to efgartigimod alfa would increase in patients with renal impairment. However, the magnitude of the increase in exposure in patients with mild renal impairment was minimal, suggesting that the contribution of renal excretion to the clearance of efgartigimod alfa was small, and there were no problems with the safety or tolerability of efgartigimod alfa 25 mg/kg in Study 1501. In Study 1704, the incidence of adverse events did not substantially differ between patients with normal renal function and patients with renal impairment. Given these, despite limited data from patients with moderate renal impairment and the absence of data from patients with severe renal impairment, efgartigimod alfa can be administered to patients with renal impairment, including severe cases, without adjusting the dosage regimen. However, due to the limited data from patients with moderate or severe renal impairment who received efgartigimod alfa in the clinical studies, a caution will be given in the package insert against the possible increase in exposure to efgartigimod alfa in patients with renal impairment.

PMDA's view:

- Based on the data used in the population pharmacokinetic analysis, eGFR was selected as a covariate, based on which the exposure to efgartigimod alfa was estimated to increase in patients with mild renal impairment. The urinary excretion rate of efgartigimod alfa in healthy subjects was <0.1%, suggesting minimal contribution of renal excretion to the clearance of efgartigimod alfa. Nevertheless, the molecular weight of efgartigimod alfa is within the range considered to be adequately filtered in glomeruli, and patients with renal impairment have been reported to have a decreased clearance of fragment preparations that have a molecular weight similar to that of efgartigimod alfa (*Clin Pharmacokinet.* 2017:56;41-54, *Br J Clin Pharmacol.* 1997:44;135-8).
- The population pharmacokinetic analysis was performed based on limited data from patients with moderate renal impairment, and no data were available from patients with severe renal impairment. Accordingly, the impact of renal function on the pharmacokinetics of efgartigimod alfa remains unclear.
- In this view, the pharmacokinetics of efgartigimod alfa may be affected by renal impairment. Therefore, there will be no problem with adding cautionary notes in the package insert that exposure to efgartigimod alfa may increase in patients with renal impairment, and that there are limited data from patients with moderate or severe renal impairment treated with efgartigimod alfa.

6.R.4 Pharmacokinetic drug interactions

PMDA asked the applicant to explain the pharmacokinetic interactions of efgartigimod alfa and the appropriateness of the proposed cautionary advice.

The applicant's explanation about the interactions between efgartigimod alfa and other drugs that bind to human FcRn:

- Efgartigimod alfa, a human IgG1 antibody Fc fragment engineered to increase binding affinity for human FcRn at both neutral and acidic pH, may affect the pharmacokinetics of other gMG medications that bind to human FcRn, such as IVIg (an immunoglobulin preparation) and eculizumab (a monoclonal antibody preparation).
- There is no clinical study results of the concurrent use of efgartigimod alfa and IVIg or eculizumab. However, in the pharmacokinetic drug-interaction study in transgenic humanized FcRn mice (CTD 4.2.1.4-1) receiving efgartigimod alfa with IVIg simultaneously (simultaneous administration) or 2 days before the administration of IVIg (sequential administration), efgartigimod alfa affected IgG concentrations, and the decreased total IgG concentration after the IVIg administration returned to baseline in a shorter time with simultaneous administration than with sequential administration [see Section 3.4]. Nevertheless, the effect of efgartigimod alfa depends on the magnitude of the contribution of FcRn to the pharmacokinetics of the concomitant antibody drug, etc., which precludes a quantitative extrapolation of the study results to humans.
- In Cycle 1 of the global phase III study (CTD 5.3.5.1-2, Study 1704), serum efgartigimod alfa concentration was 253 μg/mL immediately after the last dose and declined to 3.24 μg/mL 2 weeks after the last dose. The decreased total IgG concentration began to increase approximately 2 weeks after the last dose [Figure 1]. These results suggest that efgartigimod alfa no longer have effects on the catabolism of IgG, allowing IgG

degradation rate to be normalized 2 weeks after the last dose.

- These findings indicate that efgartigimod alfa, in its concurrent use with a drug that binds to human FcRn such as IVIg and eculizumab, may accelerate the clearance of the concomitant drug from the body and affect the pharmacokinetics of the drug. Therefore, the use of a drug that binds to human FcRn, such as IVIg and eculizumab, must began ≥2 weeks after the last dose of efgartigimod alfa, and such advice should be noted in the package insert.

The applicant's explanation about the interaction between efgartigimod alfa and hemocatharsis:

- Hemocatharsis used in the treatment of gMG is an extracorporeal therapy that discards plasma and its constituents from the circulation to remove pathogenic IgG autoantibodies or complements. Hemocatharsis is thought to remove proteins with a molecular weight of ≥15 kDa, such as immunoglobulins, cytokines, antigen-antibody complexes, and albumin (*Clin J Am Soc Nephrol.* 2014;9:181-90).
- There are no data from clinical studies in which hemocatharsis was performed during treatment with efgartigimod alfa. However, efgartigimod alfa, a molecular weight of approximately 54 kDa, is highly likely to be removed from the circulation by hemocatharsis. Therefore, the package insert will provide a cautionary note against hemocatharsis performed during treatment with efgartigimod alfa, which may decrease the serum efgartigimod alfa concentration, consequently attenuating its effect.

PMDA's view:

- Efgartigimod alfa is a human IgG antibody fragment engineered to increase binding affinity for human FcRn, and acts as an antagonist against FcRn. Thus, there is no problem in
- the applicant's explanation about the possible impact of efgartigimod alfa on the pharmacokinetics of drugs that bind to human FcRn.
- The half-life of efgartigimod alfa is approximately 3.5 to 4.3 days, and the serum efgartigimod alfa concentration declined sufficiently by approximately 2 weeks after the last dose. Accordingly, there is no problem with adding cautionary notes in the package insert that treatment with drugs binding to human FcRn, such as IVIg and eculizumab must begin at ≥2 weeks after the last dose of efgartigimod alfa, and that the effects of efgartigimod alfa may be attenuated by hemocatharsis.

6.R.5 Immunogenicity

The applicant's explanation about the immunogenicity of efgartigimod alfa:

- The percentages of study subjects who tested positive for ADAs after the administration of efgartigimod alfa were 9.1% (4 of 44 subjects) in the foreign phase I study (CTD 5.3.3.1-1, Study 1501), 23.2% (13 of 56 subjects) in the foreign phase I study (Reference CTD 5.3.3.1-2, Study 1702), 33.3% (4 of 12 patients) in the foreign phase II study (CTD 5.3.5.1-1, Study 1602), 20.5% (17 of 83 patients) in the global phase III study (CTD 5.3.5.1-2, Study 1704), and 3.3% (4 of 125 patients) in the global long-term extension study (CTD 5.3.5.2-2, Study 1705). Neutralizing antibodies were determined only in the phase III studies (Studies 1704 and 1705). Among 146 evaluated patients, 6 in Study 1704 had neutralizing antibodies.
- The impact of ADAs on the pharmacokinetics or pharmacodynamics of efgartigimod alfa was assessed. Table 28 shows the pharmacokinetic parameters of efgartigimod alfa by postdose ADA status, and Table

29 the percent changes from baseline in total IgG concentration by postdose ADA status in Study 1704. Neutralizing antibody-positive patients had slightly lower C_{max} and C_{trough} values; however, the percent decrease from baseline in total IgG concentration was similar regardless of postdose neutralizing antibody status.

Table 28. Pharmacokinetic parameters of efgartigimod alfa following multiple doses of 10 mg/kg by ADA status (Study 1704, Cycle 1)

	ADA-negative (N = 53)		ADA-positive				Neutralizing antibody-positive (N = 6)	
			Study drug-unassociated ADA-positive[a] (N = 13)		Study drug-associated ADA-positive (N = 17)			
	C_{max} (μg/mL)	C_{trough} (μg/mL)	C_{max} (μg/mL)	C_{trough} (μg/mL)	C_{max} (μg/mL)	C_{trough} (μg/mL)	C_{max} (μg/mL)	C_{trough} (μg/mL)
First dose	258.5 ± 292.4		221.9 ± 47.7		187.2 ± 49.2		169.6 ± 18.8	
	49		11		17		5	
Second dose	244.8 ± 70.3	17.0 ± 36.7	215.2 ± 94.8	11.5 ± 3.8	209.6 ± 65.6	8.1 ± 3.8	170.0 ± 54.5	6.0 ± 1.4
	49	48	12	8	16	14	4	3
Third dose	250.8 ± 84.3	14.2 ± 7.5	209.6 ± 50.9	11.1 ± 3.7	212.2 ± 51.7	10.1 ± 4.2	176.5 ± 28.4	6.8 ± 3.9
	49	47	12	10	16	14	6	6
Fourth dose	277.0 ± 243.7	14.3 ± 7.0	224.6 ± 41.9	9.8 ± 4.2	201.7 ± 80.3	10.8 ± 5.0	204.2 ± 58.7	8.6 ± 4.3
	49	47	13	10	15	16	5	6

Top, mean ± SD; bottom, n

a) Patients who tested positive for ADAs at baseline and had no increase in the antibody titer after the start of the study treatment

Table 29. Percent changes from baseline in total IgG concentration following multiple doses of efgartigimod alfa 10 mg/kg by ADA status (Study 1704)

	ADA-negative[a]					ADA-positive									
						Non-study drug-associated ADA-positive[b][c]					Study drug-associated ADA-positive[d]				
	Week 1	Week 2	Week 4	Week 8	Week 12	Week 1	Week 2	Week 4	Week 8	Week 12	Week 1	Week 2	Week 4	Week 8	Week 12
Cycle 1	-39.4 ± 1.4	-55.8 ± 1.2	-61.6 ± 1.0	-18.4 ± 2.0	-4.6 ± 2.7	-38.6 ± 4.5	-57.9 ± 2.7	-62.8 ± 2.5	-17.5 ± 5.1	-12.3 ± 5.7	37.9 ± 1.7	-52.7 ± 2.4	-63.5 ± 1.4	-21.6 ± 4.1	-6.2 ± 8.0
	53	52	51	53	26	13	13	13	13	6	17	16	16	15	5
Cycle 2	-41.8 ± 1.9	-56.3 ± 1.3	-61.2 ± 1.7	-19.4 ± 2.5	-4.6 ± 7.1	-37.0 ± 4.6	-57.4 ± 4.2	-62.0 ± 3.1	-15.0 ± 8.8	-40.8, -3.3	-38.7 ± 6.5	-55.9 ± 1.7	-60.8 ± 5.5	-17.8 ± 3.1	ND
	49	49	46	46	8	9	9	9	7	2	4	4	3	4	0

	Neutralizing antibody-positive[e]				
	Week 1	Week 2	Week 4	Week 8	Week 12
Cycle 1	-37.6 ± 2.3	-49.2 ± 5.3	-64.3 ± 3.2	-13.0 ± 7.0	ND
	6	6	5	5	0

Top, mean ± SE or individual value; bottom, n; ND, not determined

a) The total IgG concentration (mean ± SE) at baseline, 8378 ± 336 μg/mL;

b) Patients who tested positive for ADAs at baseline and had no increase in the antibody titer after the start of study treatment;

c) The total IgG concentration at baseline, 6763 ± 395 μg/mL; d) The total IgG concentration at baseline, 9144 ± 538 μg/mL;

e) The total IgG concentration at baseline was 8872 ± 654 μg/mL.

- Table 30 shows the percentages of Myasthenia Gravis Activities of Daily Living (MG-ADL) responders[29] by ADA status in Study 1704. The efficacy of efgartigimod alfa based on the percentage of MG-ADL responders did not differ substantially between ADA-positive and -negative patients. The percentage of MG-ADL responders in neutralizing antibody-positive patients was 4 of 6 patients (66.7%), suggesting no impact of neutralizing antibodies on the efficacy of efgartigimod alfa.

[29] Patients who achieved a ≥2-point decrease in the MG-ADL total score from the baseline of each treatment cycle by 1 week after the last dose of efgartigimod alfa in the cycle and maintained the decrease for ≥4 consecutive weeks

Table 30. Percentages of MG-ADL responders by ADA status (Study 1704, Cycle 1)

Anti-AChR antibody-positive subpopulation						Overall population					
ADA-negative		ADA-positive				ADA-negative		ADA-positive			
		Study Non-study drug-associated ADA-positive[a)]		Study drug-associated ADA-positive				Study Non-study drug-associated ADA-positive[a)]		Study drug-associated ADA-positive	
Placebo	Efgartigimod alfa	Placebo	Efgartigimod alfa	Placebo	Efgartigimod alfa	Placebo	Efgartigimod alfa	Placebo	Efgartigimod alfa	Placebo	Efgartigimod alfa
16/55 (29.1)	26/39 (66.7)	3/6 (50.0)	5/9 (55.6)	0/2	13/17 (76.5)	23/67 (34.3)	36/53 (67.9)	7/12 (58.3)	8/13 (61.5)	1/3 (33.3)	13/17 (76.5)

n/N (%)

a) Patients who tested positive for ADAs before the start of the study treatment and had no increase in the antibody titer after the start of the study treatment

- The safety assessments in Study 1704 revealed that the incidences of adverse events by postdose ADA status were 55.6% (5 of 9 patients) in non-study drug-associated ADA-positive patients, 82.4% (14 of 17 patients) in study drug-associated ADA-positive patients, and 76.9% (30 of 39 patients) in ADA-negative patients. Among ADA-positive patients, neither drug hypersensitivity nor anaphylaxis was reported. However, serious adverse events were reported in 2 patients (rectal adenocarcinoma and thrombocytosis in 1 patient each). A causal relationship to the study drug was ruled out by the investigator for the rectal adenocarcinoma, but could not be ruled out by the investigator for the thrombocytosis. In neutralizing antibody-positive patients, the incidence of adverse events was 50.0% (3 of 6 patients), with no serious adverse events reported.
- The above results indicate that the pharmacokinetics and pharmacodynamics of efgartigimod alfa did not clearly differ by ADA status, and that the efficacy and safety of efgartigimod alfa was not affected by ADAs. The immunogenicity of efgartigimod alfa is thus unlikely to become a clinically relevant problem.

PMDA's view:

The submitted clinical study results indicated no large impact of ADA expression during treatment with efgartigimod alfa on the pharmacokinetics, pharmacodynamics, safety, or efficacy of efgartigimod alfa. The applicant's explanation that the immunogenicity of efgartigimod alfa is unlikely to become a clinically relevant problem is thus acceptable.

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

The applicant submitted efficacy and safety evaluation data, in the form of result data from the clinical studies presented in Table 31. The applicant also submitted the results of a foreign phase I study in non-Japanese healthy adults (Reference CTD 5.3.3.1-2, Study 1702) and a phase II study in patients with primary immune thrombocytopenia (Reference CTD 5.3.5.4-1, Study 1603) as reference data. The results of key studies are described below.

Table 31. Summary of clinical efficacy and safety studies

Data category	Geographical location	Study identifier CTD	Phase	Study population	Number. of subjects/ patients enrolled	Dosage regimen	Main endpoints
Evaluation data	Foreign	Study 1501 5.3.3.1-1	I	Non-Japanese healthy adults	62	Single-ascending-dose part: A single intravenous dose of placebo, or efgartigimod alfa 0.2, 2.0, 10, 25, or 50 mg/kg Multiple-ascending-dose part: Multiple intravenous doses of placebo, or efgartigimod alfa 10 mg/kg (every 4 days or every 7 days) or 25 mg/kg (every 7 days)	Safety Pharmacokinetics
		Study 1602 5.3.5.1-1	II	Patients with gMG	24	Four once-weekly intravenous doses of placebo or efgartigimod alfa 10 mg/kg	Safety Efficacy Pharmacokinetics
	Global	Study 1704 5.3.5.1-2	III		167	Four once-weekly intravenous doses of placebo or efgartigimod alfa 10 mg/kg	Efficacy Safety Pharmacokinetics
		Study 1705 5.3.5.2-2	III (Long-term extension)		139	Four once-weekly intravenous doses of efgartigimod alfa 10 mg/kg	Safety Efficacy

7.1 Phase I study

7.1.1 Foreign phase I study (CTD 5.3.3.1-1, Study 1501, September 2015 to October 2016)

A clinical study comprising a single-ascending-dose part and a multiple-ascending-dose part was conducted to evaluate the safety and pharmacokinetics of a single intravenous dose and multiple intravenous doses of efgartigimod alfa in non-Japanese healthy adults (target sample size, 62) [for pharmacokinetic results, see Section 6.2.1].

(a) Single-ascending-dose part

A placebo-controlled, randomized, double-blind, single ascending dose study was conducted to evaluate the safety and pharmacokinetics of a single intravenous dose of efgartigimod alfa in non-Japanese healthy adults (target sample size, 30; 6 in each cohort).

Subjects in each cohort received a single intravenous dose of placebo, or efgartigimod alfa 0.2, 2.0, 10, 25, or 50 mg/kg [see Table 14]. Of 6 subjects in each cohort, 2 were randomized to receive placebo and 4 to receive efgartigimod alfa.

All 30 randomized subjects (10 in the placebo group and 20 in the efgartigimod alfa groups) were treated with the study drug and included in the safety analysis set. No subjects discontinued the study treatment.

Adverse events (including abnormal clinical laboratory values) were reported in 50.0% (5 of 10) of subjects in the placebo groups (all cohorts), 25.0% (1 of 4) of subjects in the efgartigimod alfa 0.2 mg group (Cohort 1), 50.0% (2 of 4) of subjects in the 2 mg/kg group (Cohort 2), and 50.0% (2 of 4) of subjects in the 10 mg/kg group (Cohort 3), 75.0% (3 of 4) of subjects in the 25 mg/kg group (Cohort 4), and 100% (4 of 4) of subjects in the 50 mg/kg group (Cohort 5). There were no serious adverse events including deaths. Adverse events (including abnormal clinical laboratory values) for which a causal relationship to the study drug could not be ruled out were reported in 10% (1 of 10) of subjects in the placebo group, 75.0% (3 of 4) of subjects in the 25 mg group, and 100% (4 of 4) of subjects in the 100 mg group. Common events were differential white blood cell count

abnormal (0 subjects each in the placebo, 0.2 mg/kg, 2 mg/kg, and 10 mg/kg groups, 3 subjects in the 25 mg/kg group, and 4 subjects in the 50 mg/kg group), C-reactive protein increased (0 each in the placebo, 0.2 mg/kg, 2 mg/kg, and 10 mg/kg groups, 2 in the 25 mg/group, and 4 in the 50 mg/kg group), and headache (1 in the placebo group, 0 in the 0.2 mg group, 1 in the 2 mg group, 0 in the 10 mg group, 1 in the 25 mg/kg group, and 3 in the 50 mg/kg group).

There were no clinically relevant changes in vital signs (blood pressure and pulse rate), electrocardiograms, or immunoglobulins (IgA, IgD, IgE, and IgM).

(b) Multiple-ascending-dose part

A placebo-controlled, randomized, double-blind, multiple ascending dose study was conducted to evaluate the safety and pharmacokinetics of multiple intravenous doses of efgartigimod alfa in non-Japanese healthy adults (target sample size, 32; 8 for each cohort).

Subjects in each cohort received 4 or 6 doses of placebo, efgartigimod alfa 10 mg/kg every 4 days (10 mg/kg Q4D group), efgartigimod alfa 25 mg/kg every 7 days (25 mg/kg Q7D group), or efgartigimod alfa 10 mg/kg every 7 days (10 mg/kg Q7D group) [see Table 14]. Of the 8 subjects in each cohort, 2 subjects were randomized to receive placebo and 6 to receive efgartigimod alfa.

All 32 randomized subjects (8 in the placebo group, 6 in the 10 mg/kg Q4D group, and 6 in the 25 mg/kg Q7D group [Cohort 8], 6 in the 10 mg/kg Q7D group, and 6 in the 25 mg/kg Q7D group [Cohort 10]) were treated with the study drug and included in the safety analysis set. A total of 9 subjects discontinued the study treatment. The reasons for discontinuation were consent withdrawal (1 in the 10 mg/kg Q4D group), and a serious adverse event (hyperventilation) occurring in 1 subject in Cohort 8, resulting in drug discontinuations in all of the subjects of Cohort 8[30] (2 in the placebo group and 6 in the 25 mg/kg Q7D group).

Adverse events (including abnormal clinical laboratory values) were reported in 62.5% (5 of 8) of subjects in the placebo group, 66.7% (4 of 6) of subjects in the 10 mg/kg Q4D group, 83.3% (5 of 6) of subjects in the 25 mg/kg Q7D group (Cohort 8), 66.7% (4 of 6) of subjects in the 10 mg/kg Q7D group, and 66.7% (4 of 6) of subjects in the 25 mg/kg Q7D group (Cohort 10). There were no deaths. Hyperventilation occurring in 1 subject in the 25 mg/kg Q7D group (Cohort 8) was reported as serious adverse event other than death, for which a causal relationship to the study drug was considered unlikely.[31] Adverse events (including abnormal clinical laboratory values) for which a causal relationship to the study drug could not be ruled out were reported in 37.5% (3 of 8) of subjects in the placebo group, 33.3% (2 of 6) of subjects in the 10 mg/kg Q4D group, 33.3% (2 of 6) of subjects in the 25 mg/kg Q7D group (Cohort 8), 33.3% (2 of 6) of subjects in

30) All subjects in Cohort 8 discontinued the study treatment due to a serious adverse event in 1 subject in the cohort. When the serious adverse event occurred, 4 subjects (including the subject experiencing the serious adverse event) in Cohort 8 had received 1 dose of the study drug, while the other 4 subjects had received 2 doses of the study drug. After the discontinuation of Cohort 8, a new cohort with the same dosage regimen as that used in Cohort 8 was initiated as Cohort 10.

31) The causality of adverse events to the study drug was assessed by the investigators as any of "unrelated," "unlikely," "possibly," "probably," or "certainly." Adverse events assessed as "certainly," "probably," and "possibly" were defined as adverse events for which a causal relationship to the study drug could not be ruled out.

the 10 mg/kg Q7D group, and 50% (3 of 6) of subjects in the 25 mg/kg Q7D group (Cohort 10). The common events were headache (1 in the placebo group, 1 in the 10 mg/kg Q4D group, 0 in the 25 mg/kg Q7D group [Cohort 8], 0 in the 10 mg/kg Q7D group, and 3 in the 25 mg/kg Q7D group [Cohort 10]), feeling cold (0, 0, 1, 0, and 2), and fatigue (1, 0, 0, 0, and 2).

The vital sign (blood pressure, pulse rate, and body temperature) assessment revealed body temperature increased in 2 subjects (1 each in the 10 mg/kg Q4D group and the 25 mg/kg Q7D group [Cohort 10]). A causal relationship to the study drug could not be ruled out in the subject in the 25 mg/kg Q7D group (Cohort 10). There were no clinically relevant changes in electrocardiograms or immunoglobulins (IgA, IgD, IgE, and IgM).

7.2 Phase II study

7.2.1 Foreign phase II study (CTD 5.3.5.1-1, Study 1602, September 2016 to October 2017)

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in 8 countries[32)] to evaluate the safety, efficacy, and pharmacokinetics of efgartigimod alfa in non-Japanese patients with gMG[33)] (target sample size, 24; 12 each in the placebo group and the efgartigimod alfa group) [for pharmacokinetic results, see Section 6.2.2].

This study comprised the treatment period (3 weeks) and the follow-up period (8 weeks).

Patients received 4 intravenous doses (2-hour infusion) of placebo or efgartigimod alfa 10 mg/kg at weekly intervals.[34)] Any change in the types or dosage regimens of the concomitant standard-of-care medications (cholinesterase inhibitor, corticosteroids, and/or nonsteroidal immunosuppressants) was prohibited during the study.

All 24 randomized patients (12 in the placebo group and 12 in the efgartigimod alfa group) were included in the safety analysis set and defined as the full analysis set (FAS) for the efficacy analyses. One patient (0 in the placebo group, 1 in the efgartigimod alfa group) discontinued study treatment because of lack of efficacy.

Table 32 presents the results for the efficacy endpoints, changes from baseline in MG-ADL total score[35)] and Quantitative Myasthenia Gravis (QMG) total score.[36)]

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32) Belgium, Canada, Italy, Netherlands, Poland, Spain, Sweden, and the US

33) The main inclusion criteria were: (a) meeting the Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II, III, or IVa for the diagnosis of MG; (b) having MG-ADL total scores of ≥5 points at screening and baseline, with >50% of these total scores attributable to non-ocular items; (c) having been on stable doses of the standard-of-care treatments for the primary disease (cholinesterase inhibitors, corticosteroids, and/or nonsteroidal immunosuppressants) prior to screening; and, (d) testing positive for anti-AChR antibodies.

34) The dose of efgartigimod alfa for patients weighing ≥120 kg was 1200 mg.

35) A patient-reported outcome measure assessing 8 items of MG symptoms including ocular muscles (double vision, eyelid ptosis), bulbar symptoms (talking, chewing, swallowing), respiratory muscles (breathing), and impaired gross motor or limb muscles (impaired ability to brush teeth or comb hair, impaired ability to arise from a chair) on a 4-point scale of 0 (normal) to 3 (most severe)

36) A physician-scoring outcome measure for muscle weakness and fatigability primarily based on the results of quantitative examinations for 13 items including ocular muscles (double vision, eyelid ptosis), facial muscles (facial muscle strength), bulbar symptoms (swallowing of 4 oz. water, speech after counting aloud from 1 to 50), gross motor (right hand grip, left hand grip, right arm outstretched, left arm outstretched, right leg outstretched, and left leg outstretched), axial muscles (head lifted), and respiratory muscles (forced vital capacity) assessing on a 4-point scale of 0 (normal) to 3 (most severe)

Table 32. Changes from baseline in MG-ADL total score and QMG total score (Study 1602, FAS)

		MG-ADL total score		QMG total score	
		Placebo	Efgartigimod alfa	Placebo	Efgartigimod alfa
Baseline[a)]		8.0 ± 2.17 (12)	8.0 ± 3.02 (12)	11.8 ± 5.39 (12)	14.5 ± 6.26 (12)
Change from baseline	Day 8[b)]	-0.7 ± 1.56 (12)	-1.9 ± 2.75 (12)	0.0 ± 2.22 (12)	-2.8 ± 3.13 (12)
	Day 15[c)]	-2.2 ± 2.08 (12)	-2.8 ± 2.70 (12)	-1.8 ± 3.08 (12)	-4.0 ± 4.29 (12)
	Day 22[d)]	-2.5 ± 2.50 (12)	-3.5 ± 2.84 (12)	-1.8 ± 3.91 (12)	-4.0 ± 4.55 (12)
	Day 29	-2.3 ± 2.72 (11)	-4.1 ± 2.64 (12)	-1.4 ± 3.72 (11)	-4.9 ± 4.94 (12)
	Day 36	-2.1 ± 2.43 (12)	-4.2 ± 3.30 (12)	-1.9 ± 3.37 (12)	-5.7 ± 5.97 (12)
	Day 43	-2.4 ± 2.69 (11)	-3.8 ± 2.72 (12)	-2.1 ± 4.55 (11)	-4.6 ± 5.73 (12)
	Day 50	-2.9 ± 2.96 (10)	-4.4 ± 3.53 (11)	-2.1 ± 3.95 (9)	-5.5 ± 5.84 (10)
	Day 64	-1.8 ± 3.55 (12)	-3.4 ± 3.27 (10)	-1.8 ± 4.59 (10)	-4.5 ± 6.42 (10)
	Day 78	-1.8 ± 4.22 (12)	-3.5 ± 3.50 (11)	-2.1 ± 5.07 (10)	-4.8 ± 7.67 (10)

Mean ± SD (n)
a) Immediately before the first dose (Day 1); b) Second dose; c) Third dose; d) Fourth dose

Adverse events (including abnormal clinical laboratory values) were reported in 83.3% (10 of 12) of patients in the placebo group and 83.3% (10 of 12) of patients in the efgartigimod alfa group. There were no deaths or serious adverse events. Adverse events for which a causal relationship to the study drug could not be ruled out were reported in 25.0% (3 of 12) of patients in the placebo group and 66.7% (8 of 12) of patients in the efgartigimod alfa group. The common events were headache (1 patient in the placebo group, 3 patients in the efgartigimod alfa group) and monocyte count decreased (0, 2).

There were no clinically relevant changes in vital signs (blood pressure, pulse rate, and body temperature), electrocardiograms, or immunoglobulins (IgA, IgD, IgE, and IgM).

7.3 Phase III studies

7.3.1 Global phase III study (CTD 5.3.5.1-2, Study 1704, August 2018 to April 2020)

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in 15 countries[37)] to evaluate the efficacy, safety, and pharmacokinetics of efgartigimod alfa in Japanese and non-Japanese patients with gMG[38)] (target sample size, 150[39)]; 75 each for the placebo group and the efgartigimod alfa group) [for pharmacokinetic results, see Section 6.2.2].

In the study, an 8-week treatment period (3-week treatment plus 5-week follow-up) followed by an inter-cycle observation period was defined as 1 cycle. Patients who met the prespecified criteria[40)] during the intertreatment

37) Japan, Belgium, Canada, Czech, Denmark, France, Georgia, Germany, Hungary, Italy, Netherlands, Poland, Russia, Serbia, and the US

38) The main inclusion criteria were: (a) meeting the criteria for MGFA Clinical Classification Class II, III, or IVa for the diagnosis of MG; (b) having MG-ADL total scores of ≥5 points at screening and baseline, with >50% of these total scores attributable to non-ocular items; (c) having been on stable doses of the standard-of-care treatments for the primary disease (cholinesterase inhibitors, corticosteroids, and/or nonsteroidal immunosuppressants) prior to screening.
Patients who received IVIg or hemocatharsis within 1 month prior to screening, patients who used monoclonal antibodies (eculizumab, rituximab) within 6 months prior to the first dose of the study drug, patients who had been demonstrated to be unresponsive to plasma exchange, and those with a total IgG concentration of <6 g/L at screening were excluded.

39) Eligible patients were randomized at a 1:1 ratio to receive efgartigimod alfa or placebo according to 3 stratification factors, i.e., (a) ethnicity (Japanese vs. non-Japanese), (b) anti-AChR antibody status (positive vs. negative), and (c) the type of standard-of-care treatment (any nonsteroidal immunosuppressant vs. no nonsteroidal immunosuppressant). The maximum percentage of anti-AChR antibody-negative patients among all patients was set to be 20%. Assuming that the percentage of MG-ADL responders in the placebo group was 30%, and the percentage of MG-ADL responders in the efgartigimod alfa group was 29% higher than that in the placebo group (the percentage in the efgartigimod alfa group was 35% and 5% higher than those in the placebo group among anti-AChR antibody-positive patients [80% of the overall population] and anti-AChR antibody-negative patients [20% of the overall population], respectively), a total sample size of 150 patients would be needed to detect a significant between-group difference at a 2-sided significant level of 0.05, with a power of 90%, and allowing for a 10% dropout rate.

40) Patients were allowed to start a new treatment cycle, if all of the following criteria (a) to (d) were met during the intertreatment cycle period:

cycle period were allowed to start a new treatment cycle and continue up to 3 cycles (28 weeks) of study treatment.

During the 3-week treatment period of each cycle, patients received intravenous doses of placebo or efgartigimod alfa 10 mg/kg[34)] (by 1-hour infusion) once-weekly for 4 times. Any change in the types or dosage regimens of the concomitant standard-of-care medications (cholinesterase inhibitors, corticosteroids, and/or nonsteroidal immunosuppressants) was prohibited during the study. Rescue therapy[41)] was permitted at the discretion of the investigators for patients presenting with clinically deteriorated symptoms of MG (new or worsening of respiratory/bulbar symptoms, or ≥2-point worsening of MG-ADL total score attributable to any non-ocular items) who were likely to fall into a critical condition without it. Patients receiving rescue therapy were withdrawn from the study.

All 167 patients (83 in the placebo group and 84 in the efgartigimod alfa group) were included in the safety analysis set and defined as the modified intent-to-treat (mITT) population[42)] that was used for the efficacy analyses. Of these 167 patients, 129 (64 in the placebo group and 65 in the efgartigimod alfa group) tested positive for anti-AChR antibodies, and 38 (19 in the placebo group and 19 in the efgartigimod alfa group) tested negative. A total of 15 patients (10 in the placebo group and 5 in the efgartigimod alfa group) discontinued the study treatment. Common reasons for discontinuation were adverse events in 5 patients (2 in the placebo group, 3 in the placebo group), of rescue therapy in 3 patients (2, 1), and consent withdrawal in 3 patients (3, 0). The numbers of patients receiving 1 cycle, 2 cycles, and 3 cycles of the study treatment were similar in the placebo group and the efgartigimod group (1 cycle, 83 in the placebo group vs. 84 in the efgartigimod alfa group; 2 cycles, 57 vs. 63; 3 cycles, 3 vs. 7).

Table 33 presents the results of the primary endpoint, the percentage of MG-ADL responders[29)] during the first treatment cycle in the anti-AChR antibody-positive subpopulation. A statistically significant difference was observed between the efgartigimod alfa group and the placebo group. The percentage of MG-ADL responders during the first treatment cycle in the overall population, which included both anti-AChR antibody-positive and -negative patients, was evaluated as a secondary endpoint (Table 33).

(a) The patient had completed the previous treatment cycle;
(b) The patient had an MG-ADL total score of ≥5 points with >50% of the total score attributable to non-ocular symptoms;
(c) The patient was able to start the new treatment cycle within 127 days after the last dose and complete the treatment cycle within the timeframe of Study 1704 (26 weeks); and,
(d) The patient was identified as an MG-ADL responder in the previous treatment cycle but did not show a decrease of ≥2 points in the MG-ADL total score as compared with the baseline score of the previous treatment cycle.

41) Rescue therapy was limited to plasma exchange, IVIg, immunoadsorption, an increased dose of the current corticosteroid, and a new type of corticosteroid.

42) Patients who had the MG-ADL total score at baseline and at ≥1 postbaseline timepoints

Table 33. Percentages of MG-ADL responders during the first treatment cycle in the anti-AChR antibody-positive subpopulation and the overall population (Study 1704, mITT)

	Treatment	N	MG-ADL responders	Percentage of MG-ADL responders	Odds ratio [95% CI][a)]	*P*-value[a),b)]
Anti-AChR antibody-positive	Placebo	64	19	29.7% (19/64 patients)	4.95 [2.21, 11.53]	<0.0001
	Efgartigimod alfa	65	44	67.7% (44/65 patients)		
Overall population[c)]	Placebo	83	31	37.3% (31/83 patients)	3.70 [1.85, 7.58]	<0.0001
	Efgartigimod alfa	84	57	67.9% (57/84 patients)		

a) A logistic regression model stratified by ethnicity (Japanese vs. non-Japanese) and standard-of-care treatments for gMG (any nonsteroidal immunosuppressant vs. no nonsteroidal immunosuppressant), including the baseline MG-ADL total score as a covariate. In the analysis of the overall population, anti-AChR antibody status (positive vs. negative) was added to the stratification factors.
b) Two-sided exact test with a 2-sided significance level of 5%; an adjustment for multiplicity for the primary and secondary endpoints was made by using a serial gate keeping strategy, where the endpoints were tested in a prespecified hierarchical order.
c) The percentage of MG-ADL responders in the overall population, including both anti-AChR antibody-positive and -negative patients was evaluated as a secondary endpoint.

Adverse events (including abnormal clinical laboratory values) were reported in 84.3% (70 of 83) of patients in the placebo group and 77.4% (65 of 84) of patients in the efgartigimod alfa group. There were no deaths. Table 34 presents the incidences of serious adverse events other than deaths.

Table 34. Incidences of serious adverse events other than deaths (Study 1704, safety analysis set)

Placebo	Myasthenia gravis/therapeutic product ineffective, myasthenia gravis crisis/upper respiratory tract infection, spinal ligament ossification/procedural pain, myasthenia gravis, myocardial ischaemia, atrial fibrillation, and spinal compression fracture in 1 patient each (7 patients in total)
Efgartigimod alfa	Myasthenia gravis, thrombocytosis,* depression, and rectal adenocarcinoma in 1 patient each (4 patients in total)

*An event for which a causal relationship to the study drug could not be ruled out

Adverse events (including abnormal clinical laboratory values) for which a causal relationship to the study drug could not be ruled out were reported in 26.5% (22 of 83) of patients in the placebo group and 31.0% (26 of 84) of patients in the efgartigimod alfa group. The common events were headache (10 patients in the placebo group, 10 patients in the efgartigimod alfa group), procedural headache (1, 4), nausea (5, 3), blepharospasm (0, 2), fatigue (0, 2), hypoaesthesia (0, 2), dizziness (3, 1), and abdominal pain (2, 1).

There were no clinically relevant changes in vital signs (blood pressure, pulse rate, and body temperature). The electrocardiography assessment revealed that 1 patient in the efgartigimod alfa group had an increased QTcF interval of >480 to ≤500 milliseconds after the third dose of efgartigimod alfa in the second treatment cycle, which was not associated with any medical history or caused any adverse events, and the study treatment continued. Thus, the event was not considered clinically relevant.

7.3.2 Global long-term extension study (CTD 5.3.5.2-2, Study 1705, ongoing since March 2019 [data cutoff in October 2020])

An open-label, uncontrolled study was conducted to evaluate the long-term safety, tolerability, and efficacy of efgartigimod alfa in patients who participated in the global phase III study (Study 1704) and met the eligibility criteria for transfer to the extension study[43)] (target sample size, 167).

43) The main eligibility criteria were: (a) having continued Study 1704 until Day 182, which was the end of the study; (b) having met the criteria for a new treatment cycle during the intertreatment cycle period [see footnote 40) of this report] but been unable to complete the new treatment cycle until Day 182, which was the end of Study 1704.

Each cycle comprised a 3-week treatment period and an intertreatment cycle period (with a visit frequency of 4 weeks). If the prespecified criteria[44)] were met in the intertreatment cycle period in Part A of the study, the patient was allowed to start a new treatment cycle. The maximum duration of the study, which consisted of Part A (1 year, approximately 7 cycles) and Part B (≤2 years), was 3 years. As of the data cutoff in October 2020, a maximum of 8 cycles has been completed across Parts A and B.[45)]

During the 3-week treatment period of each cycle, patients received 4 intravenous doses of efgartigimod alfa 10 mg/kg[34)] (by a 1-hour infusion) at weekly intervals. In Part A, any change in the types or dosage regimens of the concomitant standard-of-care medications (cholinesterase inhibitors, corticosteroids, and/or nonsteroidal immunosuppressants) was prohibited during the 3-week treatment period and the subsequent week. However, dose reductions of the concomitant standard-of-care medications during the intertreatment cycle period (1 week after the last dose of efgartigimod alfa or later) were allowed.[46)] In Part B, patients were able to start a new treatment cycle at the discretion of the investigator or sub-investigator after ≥4 weeks from the last dose in the previous treatment period.

Of 151 patients enrolled in Part A and Part B, 139 patients (66 in the placebo/efgartigimod alfa group and 73 in the efgartigimod alfa/efgartigimod alfa group) were treated with efgartigimod alfa and were included in the safety analysis set and the efficacy analysis set. Of these 139 patients, 106 patients (48 in the placebo/efgartigimod alfa group, 58 in the efgartigimod alfa/efgartigimod alfa group) tested positive for anti-AChR antibodies and 33 patients (18, 15) tested negative. A total of 21 patients (11, 10) discontinued study treatment. Common reasons for discontinuation were consent withdrawal in 5 patients (3, 2), treatment failure in 5 patients (4, 1), adverse events in 3 patients (0, 3), and death in 3 patients (1, 2).

Tables 35 and 36, respectively, present the results for the efficacy endpoint, the changes from baseline to Week 3 (the last dose of efgartigimod alfa) in MG-ADL total score and in QMG total score in each treatment cycle. Both the anti-AChR antibody-positive subpopulation and the overall population showed improvement.

44) Patients who met all of the following criteria (a) to (c) were allowed to start a new treatment cycle:
(a) having completed the previous treatment period; (b) having an MG-ADL total score of ≥5 points, with ≥ 50% of the total score attributable to non-ocular symptoms; (c) showing a decrease of <2 points in MG-ADL total score at the time points (i) or (ii) below, as compared with baseline.
(i) For patients newly starting treatment with efgartigimod alfa in Study 1705, before the start of study treatment in the last treatment cycle of Study 1704; ii) For patients receiving the second or subsequent doses of efgartigimod alfa in Study 1705, before the start of treatment with efgartigimod alfa in the previous treatment period.

45) As of the data cutoff in October 2020, 139 patients had completed 1 cycle, 125 patients 2 cycles, 106 patients 3 cycles, 81 patients 4 cycles, 62 patients 5 cycles, 37 patients 6 cycles, 17 patients 7 cycles, and 12 patients 8 cycles.

46) In Part B of Study 1705, changes in the types or dosage regimens of the concomitant standard-of-care treatments (cholinesterase inhibitors, corticosteroids, and/or nonsteroidal immunosuppressants) used in clinical practice were allowed.

Table 35. Changes in MG-ADL total score from baseline to Week 3 (the last dose of efgartigimod alfa) in each treatment cycle in the anti-AChR antibody-positive subpopulation and the overall population (Study 1705)

		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7
Anti-AChR antibody-positive subpopulation	Placebo/ efgartigimod alfa[a)]	9.0 ± 0.37(48) 9.0 (5, 16)	9.3 ± 0.39(46) 9.0 (5, 17)	9.2 ± 0.49(37) 9.0 (5, 17)	10.0 ± 0.66(29) 9.0 (5, 16)	10.0 ± 0.74(21) 9.0 (5, 15)	10.0 ± 0.96(13) 9.0 (6, 18)	13.0 ± 1.87(5) 11.0 (9, 18)
		-4.0 ± 0.41(47) -3.0 (-10, 1)	-4.4 ± 0.43(44) -4.0 (-9, 2)	-4.2 ± 0.53(36) -4.0 (-12, 1)	-4.8 ± 0.65(28) -4.0 (-12, 0)	-4.6 ± 0.63(20) -4.0 (-11, 0)	-6.3 ± 1.57(8) -5.0 (-15, -2)	-9.5 ± 2.33(4) -9.5 (-15, -4)
	Efgartigimod alfa/ efgartigimod alfa[a)]	10.2 ± 0.43(58) 10.0 (5, 18)	10.4 ± 0.51(49) 10.0 (5, 18)	10.8 ± 0.55(45) 11.0 (5, 18)	11.4 ± 0.62(34) 11.5 (5, 19)	11.0 ± 0.75(26) 11.0 (5, 18)	11.2 ± 1.11(11) 11.0 (6, 17)	12.3 ± 1.23(6) 12.5 (8, 16)
		-6.0 ± 0.49(56) -6.0 (-16, 1)	-6.4 ± 0.57(48) -6.0 (-15, 1)	-6.5 ± 0.54(42) -6.5 (-13, 1)	-7.6 ± 0.69(32) -8.0 (-13, 1)	-7.5 ± 0.73(22) -7.0 (-14, 0)	-7.7 ± 1.12(10) -7.5 (-13, -1)	-8.5 ± 1.41(6) -9.5 (-12, -2)
Overall population	Placebo/ efgartigimod alfa[a)]	9.5 ± 0.37(66) 9.0 (5, 19)	9.8 ± 0.37(62) 9.5 (5, 18)	9.8 ± 0.43(53) 9.0 (5, 17)	10.2 ± 0.54(40) 10.5 (5, 16)	10.3 ± 0.57(30) 11.0 (5, 15)	10.4 ± 0.68(22) 10.5 (5, 18)	12.9 ± 1.03(10) 13.0 (9, 18)
		-4.1 ± 0.41(65) -3.0 (-19, 1)	-4.6 ± 0.41(60) -4.0 (-13, 2)	-4.4 ± 0.47(50) -4.0 (-14, 1)	-4.7 ± 0.57(38) -4.0 (-12, 0)	-4.9 ± 0.51(29) -5.0 (-11, 0)	-5.6 ± 0.91(15) -5.0 (-15, -2)	-8.3 ± 1.49(8) -8.5 (-15, -2)
	Efgartigimod alfa/ efgartigimod alfa[a)]	10.4 ± 0.38(73) 10.0 (5, 18)	10.6 ± 0.44(63) 11.0 (5, 18)	10.9 ± 0.50(53) 11.0 (5, 18)	11.5 ± 0.57(41) 11.0 (5, 19)	11.2 ± 0.67(32) 11.0 (5, 18)	10.8 ± 0.94(15) 10.0 (6, 17)	12.7 ± 1.11(7) 13.0 (8, 16)
		-6.1 ± 0.45(71) -6.0 (-16, 1)	-6.3 ± 0.50(60) -6.0 (-15, 1)	-6.5 ± 0.52(49) -7.0 (-15, 1)	-7.5 ± 0.63(39) -7.0 (-14, 1)	-7.4 ± 0.70(28) -6.5 (-14, 0)	-7.3 ± 1.17(12) -7.5 (-13, 0)	-8.5 ± 1.41(6) -9.5 (-12, -2)

Mean ± SE (n), median (minimum, maximum)

Top, baseline MG-ADL total score; bottom, the change in MG-ADL total score from baseline to Week 3 (the last dose of efgartigimod alfa)

a) The placebo/efgartigimod alfa group received placebo in Study 1704, and started to receive efgartigimod alfa in Cycle 1 of Study 1705. The efgartigimod alfa/efgartigimod alfa group had received efgartigimod alfa in Study 1704, but the table indicates treatment cycles in Study 1705 alone.

Table 36. Changes in QMG total score from baseline to Week 3 (the last dose of efgartigimod alfa) in each treatment cycle in the anti-AChR antibody-positive subpopulation and the overall population (Study 1705)

		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7
Anti-AChR antibody-positive	Placebo/ efgartigimod alfa[a)]	15.9 ± 0.65(48) 16.5 (6, 25)	16.4 ± 0.72(46) 16.0 (8, 27)	15.4 ± 0.81(36) 15.0 (7, 25)	16.6 ± 1.10(26) 17.0 (6, 25)	16.8 ± 1.16(19) 18.0 (7, 24)	18.4 ± 1.52(12) 17.0 (13, 33)	21.4 ± 2.42(5) 22.0 (13, 28)
		-4.2 ± 0.52(46) -3.0 (-13, 3)	-4.8 ± 0.52(41) -4.0 (-13, 0)	-3.3 ± 0.64(33) -3.0 (-14, 3)	-3.3 ± 0.66(25) -3.0 (-9, 2)	-2.9 ± 0.87(16) -2.0 (-8, 2)	-6.4 ± 1.95(7) -5.0 (-17, -2)	-6.3 ± 3.38(3) -4.0 (-13, -2)
	Efgartigimod alfa/ efgartigimod alfa[a)]	15.3 ± 0.84(58) 15.0 (4, 34)	16.2 ± 0.92(49) 16.0 (4, 34)	16.0 ± 0.98(43) 16.0 (0, 30)	14.9 ± 1.12(31) 14.0 (1, 30)	16.4 ± 1.40(20) 16.0 (5, 30)	14.5 ± 1.95(8) 16.5 (2, 20)	17.2 ± 1.45(6) 17.5 (11, 21)
		-5.1 ± 0.62(54) -4.5 (-16, 3)	-5.9 ± 0.67(45) -5.0 (-17, 2)	-5.8 ± 0.83(34) -5.0 (-18, 2)	-5.8 ± 1.08(23) -6.0 (-16, 3)	-5.6 ± 0.96(15) -4.0 (-13, -1)	-6.2 ± 1.25(6) -6.0 (-10, -2)	-5.7 ± 1.09(6) -6.0 (-8, -1)
Overall population	Placebo/ efgartigimod alfa[a)]	16.4 ± 0.58(66) 17.0 (6, 26)	16.5 ± 0.62(62) 16.5 (8, 27)	15.8 ± 0.63(52) 15.5 (7, 25)	16.5 ± 0.99(36) 18.0 (1, 25)	17.0 ± 0.92(26) 17.5 (7, 25)	18.6 ± 1.12(19) 18.0 (13, 33)	20.8 ± 1.35(10) 22.0 (13, 28)
		-4.5 ± 0.43(64) -4.0 (-13, 3)	-4.3 ± 0.46(56) -4.0 (-13, 3)	-3.8 ± 0.59(46) -3.0 (-15, 3)	-3.4 ± 0.54(32) -3.0 (-9, 2)	-3.3 ± 0.70(23) -2.0 (-9, 2)	-6.0 ± 1.35(12) -5.0 (-17, -1)	-7.0 ± 1.83(6) -5.5 (-13, -2)
	Efgartigimod alfa/ efgartigimod alfa[a)]	15.1 ± 0.73(73) 15.0 (1, 34)	16.0 ± 0.80(63) 16.0 (4, 34)	16.1 ± 0.88(51) 16.0 (0, 30)	14.8 ± 1.02(38) 14.5 (1, 30)	16.0 ± 1.18(25) 16.0 (5, 30)	14.0 ± 1.48(11) 15.0 (2, 20)	17.2 ± 1.45(6) 17.5 (11, 21)
		-5.1 ± 0.57(69) -4.0 (-19, 3)	-5.8 ± 0.59(55) -5.0 (-17, 2)	-5.9 ± 0.74(41) -5.0 (-18, 2)	-5.9 ± 0.96(27) -6.0 (-16, 3)	-5.7 ± 0.87(18) -4.0 (-13, -1)	-6.2 ± 1.25(6) -6.0 (-10, -2)	-5.7 ± 1.09(6) -6.0 (-8, -1)

Mean ± SE (n), median (minimum, maximum)

Top, QMG total score at baseline; bottom, the change in QMG total score from baseline to Week 3 (the last dose of efgartigimod alfa)

a) The placebo/efgartigimod alfa group received placebo in Study 1704, and started to receive efgartigimod alfa in Cycle 1 of Study 1705. The efgartigimod alfa/efgartigimod alfa group had received efgartigimod alfa in Study 1704, but the table indicates treatment cycles in Study 1705 alone.

Adverse events (including abnormal clinical laboratory values) were reported in 72.7% (48 of 66) of patients in the placebo/efgartigimod alfa group and 67.1% (49 of 73) of patients in the efgartigimod alfa/efgartigimod alfa group. Deaths occurred in 1 patient in the placebo/efgartigimod alfa group (acute myocardial infarction) and 3 patients in the efgartigimod alfa/efgartigimod alfa group (myasthenia gravis crisis, lung neoplasm malignant, and death in 1 each). A causal relationship to the study drug was ruled out for all events. Table 37 presents the incidences of serious adverse events other than deaths. A causal relationship to the study drug was ruled out for all events.

Table 37. Incidences of serious adverse events other than deaths

Placebo/ efgartigimod alfa	Myasthenia gravis crisis/pneumonia, prostate cancer/bladder neck obstruction, myasthenia gravis, pancreatic carcinoma, and retinal detachment in 1 patient each (5 patients in total)
Efgartigimod alfa/ efgartigimod alfa	COVID-19 in 2 patients, and pneumonia aspiration/pneumonia escherichia/shock/stupor, myasthenia gravis/COVID-19 pneumonia, dysentery/irritable bowel syndrome, squamous cell carcinoma of the vulva, myasthenia gravis, anaemia, diarrhoea, and spinal compression fracture in 1 patient each (10 patients in total)

Adverse events (including abnormal clinical laboratory values) for which a causal relationship to the study drug could not be ruled out were reported in 24.2% (16 of 66) of patients in the placebo/efgartigimod alfa group and 27.4% (20 of 73) of patients in the efgartigimod alfa/efgartigimod alfa group. Common events were headache (5 patients in the placebo/efgartigimod alfa group, 7 patients in the efgartigimod alfa/efgartigimod alfa group), rash (1, 2), nausea (1, 2), chills (0, 2), blood immunoglobulin G decreased (0, 2), dizziness (0, 2), vomiting (2, 1), asthenia (2, 0), and haemoglobin decreased (2, 0).

There were no clinically relevant changes in vital signs (blood pressure, pulse rate, and body temperature) or electrocardiograms.

7.R Outline of the review conducted by PMDA

7.R.1 Global study results-based evaluations

7.R.1.1 Intrinsic and extrinsic ethnic factors

PMDA asked the applicant to explain how the intrinsic and extrinsic ethnic factors potentially affecting the efficacy or safety of efgartigimod alfa were taken into consideration, in terms of Japan's participation in the global phase III study (CTD 5.3.5.1-2, Study 1704) and the global long-term extension study (CTD 5.3.5.2-2: Study 1705).

The applicant's explanation:

- The results from the foreign phase II study (CTD 5.3.5.1-1, Study 1602) and Study 1704 showed no substantial differences in the pharmacokinetic parameters of efgartigimod alfa between Japanese and non-Japanese patients. Study 1704 also showed that the percent changes from baseline in the concentrations of total IgG and IgG subclasses did not differ substantially between Japanese and non-Japanese patients. These results suggested no particular differences in the pharmacokinetics or pharmacodynamics of efgartigimod alfa between Japanese and non-Japanese patients [see Section 6.R.1]. In addition, epidemiologic studies on IgG, which is involved in the action mechanism of efgartigimod alfa, have indicated that serum IgG concentrations differ among both Japanese (*Jpn. J. Clin. Immunol.* 1994;17:535-45) and non-Japanese individuals (*Clin Exp Immunol.* 2007;151:42-50), and the individual differences in Japanese people are generally within those in non-Japanese people, with no marked difference between the populations.
- Both in and outside Japan, the diagnosis of MG relies on symptoms (e.g., eyelid ptosis, dysphagia, limb muscle weakness, and respiratory disorder), the expression of pathological autoantibodies (e.g., anti-AChR antibodies and anti-MuSK antibodies), and neuromuscular junction disorders (e.g., edrophonium chloride test and electromyogram) (*Japanese Clinical Guidelines for Myasthenia Gravis 2014*. Nankodo Co., Ltd., 2014; *J Clin Invest*. 2006;116:2843-54), and MG symptoms are categorized using the MGFA Clinical Classification (*Neurology.* 2000;55:16-23) into 5 main classes (I to V) and several subclasses, based

on disease severity and the affected muscle groups (ocular symptoms only, mild generalized symptoms, moderate generalized symptoms, severe generalized symptoms, and MG requiring intubation; in order of increasing severity). Thus, the diagnosis of MG does not differ substantially between in and outside Japan.

- According to the National Epidemiological Survey 2018, the prevalence of MG in Japan is 23.1 per 100,000 persons (https://www.nanbyou.or.jp/entry/120), with the ocular type accounting for approximately 20% of the patients (*Clin Exp Neuroimmunol.* 2014;5:84-91; *BMC Neurol.* 2014;14:142) and the generalized type accounting for approximately 80%. Among these patients, 10.2% have a history of MG crisis (*Neurol. Therap*. 2019;36:384-6). The prevalence of MG overseas is 150 to 250 per million people, with the generalized type accounting for approximately 85% of the patients (*N Engl J Med*. 2016;375:2570-81), and 15% to 20% of the patients have a history of MG crisis (*Neurohospitalist.* 2011;1:16-22). Thus, the epidemiology of MG, including prevalence, disease type, and the incidence of MG crisis, in Japan is similar to that in overseas.
- In Japan, the standard gMG treatment is immunotherapy with the supportive use of cholinesterase inhibitors (e.g., pyridostigmine and ambenonium). Immunotherapy for gMG begins with low-dose corticosteroids or nonsteroidal immunosuppressants (cyclosporine or tacrolimus hydrate). Patients who do not respond adequately to immunotherapy and require immediate improvements in symptoms receive a short-term treatment with IVIg or hemocatharsis (*Japanese Clinical Guidelines for Myasthenia Gravis 2014*. Nankodo Co., Ltd., 2014), and symptoms uncontrollable with IVIg or hemocatharsis are treated with eculizumab. Albeit different approval status of drugs in and outside Japan, immunotherapy with cholinesterase inhibitors, corticosteroids, or nonsteroidal immunosuppressants are recommended for the early stage of treatment for gMG, and IVIg, hemocatharsis, and eculizumab are other treatment options for patients with refractory MG who do not respond adequately to immunotherapy (*Neurology.* 2016;87:419-25; *Neurology.* 2021;96:114-22). Both in Japan and other countries, cholinesterase inhibitors are recommended for the early stage of treatment, despite slightly different clinical recognition for these drugs. Overall, there are no substantial differences in the treatment strategy for gMG between Japan and overseas.
- Based on the above, the differences in the intrinsic and extrinsic ethnic factors potentially affecting the efficacy or safety of efgartigimod alfa are considered small. Therefore, conducting the phase III studies of efgartigimod alfa (Studies 1704 and 1705) as global studies was appropriate.

PMDA's view:

The differences in intrinsic or extrinsic ethnic factors among the countries/regions participating in the phase III studies (Studies 1704 and 1705) are unlikely to become a significant problem. Therefore, there were no substantial problems with the participation of Japan in both global studies.

7.R.1.2 Efficacy evaluations, and differences in the efficacy and safety of efgartigimod alfa between Japanese and non-Japanese patients in the global phase III studies

PMDA asked the applicant to explain the efficacy evaluations and differences in the efficacy and safety of efgartigimod alfa between Japanese and non-Japanese patients in the global phase III study (CTD 5.3.5.1-2, Study 1704) and the global long-term extension study (CTD 5.3.5.2-2, Study 1705).

The applicant's explanation about the rationale for the primary and other efficacy endpoints, and the efficacy of efgartigimod alfa in Study 1704:

- The MG-ADL total score was used as the measure of the primary endpoint in Study 1704. The score is a patient-reported outcome measure that assesses the impairment of functions involved in daily life activities and is composed of a total of 8 subscores assessing various abilities in daily living, namely, talking, chewing, swallowing, breathing, impairment of ability to brush teeth or comb hair, and impairment of ability to rise from a chair, in addition to double vision and eyelid ptosis. A ≥2-point decrease in MG-ADL total score is considered a clinically significant improvement (*Neurology.* 1999;52:1487-9; *Muscle Nerve.* 2011;44:727-31), and the MG-ADL total score is widely used in the assessment of gMG both in and outside Japan (*Front Neurol.* 2020;11:596382).
- A ≥2-point decrease in MG-ADL total score can occur even in a short term (1 to 2 weeks) due to individual disease variability, psychological factors, interrater variability, etc. The primary endpoint in Study 1704 was thus set be the percentage of MG-ADL responders, where MG-ADL responders were defined as patients in whom a decrease of ≥2 points on the MG-ADL total score from baseline was achieved by 1 week after the last dose of efgartigimod alfa (Week 4) and the decrease was maintained for ≥4 consecutive weeks.
- In Study 1704, the QMG total score was evaluated as a key secondary endpoint. The QMG is a physician-scored outcome measure comprising the subscores of 13 items assessing ocular, bulbar, limb, and other functions. A ≥3-point decrease in QMG total score is considered clinically significant improvement *(Ann N Y Acad Sci.* 1988;841:769-72; *Muscle Nerve.* 2014;49:661-5). The QMG total score is widely used as an objective assessment based on quantitative test results both in and outside Japan, although it is unable to capture all possible gMG symptoms (*Front Neurol.* 2020;11:596382).
- For the efficacy evaluation using the MG-ADL total score and QMG total score in the phase III studies of efgartigimod alfa including Study 1704, assessors including investigators were explained about these scores and trained for the respective scoring methods in advance so that the homogeneity of evaluation would be achieved.
- The results of Study 1704 showed a statistically significant difference in the percentage of MG-ADL responders during the first treatment cycle in the anti-AChR antibody-positive subpopulation, which was the primary endpoint, between the efgartigimod alfa group and the placebo group. A similar tendency was shown in the percentage of MG-ADL responders in the overall population, including both anti-AChR antibody-positive and -negative patients, which was a secondary endpoint (Table 33). Table 38 presents the percentages of QMG responders[47)] in the first treatment cycle in the AChR antibody-positive subpopulation and the overall population. The efgartigimod alfa group had a higher percentage of QMG responders than the placebo group in both populations.

47) Patients in whom a decrease of ≥3 points on the QMG total score from baseline was achieved by 1 week after the last dose of the study drug and the decrease was maintained for ≥4 consecutive weeks

Table 38. Percentages of QMG responders in the first treatment cycle in the anti-AChR antibody-positive subpopulation and the overall population (Study 1704, mITT)

	Treatment	N	QMG responders	Percentage of QMG responders	Odds ratio [95% CI][a)]
Anti-AChR antibody-positive	Placebo	64	9	14.1% (9/64 patients)	10.84 [4.18, 31.20]
	Efgartigimod alfa	65	41	63.1% (41/65 patients)	
Overall population[b)]	Placebo	83	16	19.3% (16/83 patients)	7.10 [3.24, 16.49]
	Efgartigimod alfa	84	51	60.7% (51/84 patients)	

a) A logistic regression model stratified by ethnicity (Japanese vs. non-Japanese) and the standard-of-care treatments for gMG (any nonsteroidal immunosuppressant vs. no nonsteroidal immunosuppressant), including the baseline QMG total score as a covariate. In the analysis of the overall population, anti-AChR antibody status (positive vs. negative) was added to the stratification factors.
b) The percentage of QMG responders in the overall population, which included both anti-AChR antibody-positive and -negative patients, was evaluated as an exploratory endpoint.

- The efficacy of efgartigimod alfa was further evaluated in terms of MG-ADL subs-cores and QMG subscores in Study 1704. Table 39 and 40 present the changes in MG-ADL subscores and QMG subscores, respectively, from baseline to Week 4 (1 week after the last dose) of the first treatment cycle. The efgartigimod alfa group had greater changes in all of the MG-ADL subscores and QMG subscores than the placebo group, indicating the improvement of MG symptoms by efgartigimod alfa [for the efficacy of efgartigimod alfa by anti-AChR antibody status, see Section 7.R.2.1].

Table 39. Changes in MG-ADL subscores from baseline to Week 4 (1 week after the last dose) of the first treatment cycle (Study 1704, mITT, overall population[a)])

Subscores[b)]	Placebo			Efgartigimod alfa		
	Baseline	Week 4	Change	Baseline	Week 4	Change
Ocular muscles	2.2 ± 0.16 (83) 2.0 (0, 6)	2.0 ± 0.18 (79) 2.0 (0, 6)	-0.2 ± 0.13 (79) 0.0 (-3, 4)	2.5 ± 0.18 (84) 2.0 (0, 6)	1.6 ± 0.18 (80) 1.0 (0, 6)	-0.8 ± 0.14 (80) -0.5 (-5, 2)
Gross motor or limb impairment	2.7 ± 0.14 (83) 3.0 (0, 5)	2.0 ± 0.16 (79) 2.0 (0, 5)	-0.6 ± 0.13 (79) 0.0 (-4, 2)	2.6 ± 0.12 (84) 3.0 (0, 5)	1.3 ± 0.14 (80) 1.0 (0, 4)	-1.4 ± 0.14 (80) -1.0 (-4, 1)
Respiratory muscles	1.1 ± 0.06 (83) 1.0 (0, 2)	0.9 ± 0.07 (79) 1.0 (0, 2)	-0.2 ± 0.07 (79) 0.0 (-2, 1)	1.0 ± 0.06 (84) 1.0 (0, 2)	0.7 ± 0.07 (80) 1.0 (0, 2)	-0.4 ± 0.08 (80) 0.0 (-2, 1)
Bulbar symptoms	2.9 ± 0.13 (83) 3.0 (1, 6)	1.9 ± 0.16 (79) 2.0 (0, 6)	-0.9 ± 0.12 (79) -1.0 (-5, 1)	3.1 ± 0.15 (84) 3.0 (0, 6)	1.1 ± 0.15 (80) 1.0 (0, 5)	-1.9 ± 0.19 (80) -2.0 (-5, 3)

Top, mean ± SE (n); bottom, median (minimum, maximum)
a) The overall population included both anti-AChR antibody-positive and -negative patients.
b) Ocular muscles (double vision, eyelid ptosis), bulbar symptoms (talking, chewing, swallowing), respiratory muscles (breathing), and gross motor or limb impairment (impairment of ability to brush teeth or comb hair, impairment of ability to arise from a chair)

Table 40. Changes in QMG subscores from baseline to Week 4 (1 week after the last dose) of the first treatment cycle (Study 1704, mITT, overall population[a)])

Subscores[b)]	Placebo			Efgartigimod alfa		
	Baseline	Week 4	Change	Baseline	Week 4	Change
Ocular muscles	2.6 ± 0.19 (81) 3.0 (0, 6)	2.4 ± 0.19 (79) 3.0 (0, 6)	-0.1 ± 0.15 (77) 0.0 (-6, 4)	2.8 ± 0.21 (84) 3.0 (0, 6)	1.7 ± 0.20 (79) 1.0 (0, 6)	-1.0 ± 0.19 (79) -1.0 (-6, 3)
Facial muscles	1.1 ± 0.08 (81) 1.0 (0, 3)	0.9 ± 0.08 (79) 1.0 (0, 3)	-0.2 ± 0.07 (77) 0.0 (-2, 1)	1.2 ± 0.10 (84) 1.0 (0, 3)	0.6 ± 0.07 (79) 0.0 (0, 2)	-0.6 ± 0.10 (79) 0.0 (-3, 1)
Bulbar symptoms	1.2 ± 0.13 (81) 1.0 (0, 4)	0.9 ± 0.13 (79) 0.0 (0, 4)	-0.4 ± 0.12 (77) 0.0 (-3, 2)	1.5 ± 0.14 (84) 1.0 (0, 5)	0.4 ± 0.07 (79) 0.0 (0, 3)	-1.2 ± 0.14 (79) -1.0 (-4, 1)
Gross motor	8.4 ± 0.30 (81) 9.0 (3, 14)	7.7 ± 0.35 (79) 8.0 (0, 14)	-0.8 ± 0.26 (77) 0.0 (-10, 4)	8.5 ± 0.28 (84) 9.0 (1, 14)	5.9 ± 0.37 (79) 6.0 (0, 14)	-2.6 ± 0.31 (79) -2.0 (-9, 2)
Axial muscles	1.7 ± 0.07 (81) 2.0 (0, 3)	1.5 ± 0.07 (79) 2.0 (0, 3)	-0.3 ± 0.07 (77) 0.0 (-2, 1)	1.7 ± 0.07 (84) 2.0 (0, 3)	1.0 ± 0.08 (79) 1.0 (0, 3)	-0.7 ± 0.08 (79) -1.0 (-2, 1)
Respiratory muscles	0.6 ± 0.09 (81) 0.0 (0, 3)	0.6 ± 0.09 (79) 0.0 (0, 3)	0.0 ± 0.07 (77) 0.0 (-2, 2)	0.5 ± 0.08 (84) 0.0 (0, 3)	0.3 ± 0.06 (79) 0.0 (0, 2)	-0.1 ± 0.07 (79) 0.0 (-2, 1)

Top, mean ± SE (n); bottom, median (minimum, maximum)
a) The overall population included both anti-AChR antibody-positive and -negative patients.
b) Ocular muscles (double vision, eyelid ptosis), facial muscles (facial muscle strength), bulbar symptoms (swallowing of 4 oz. of water, and speech after counting aloud from 1 to 50), gross motor (right and left hand grip, arm outstretched, and leg outstretched), axial muscles (head lifted), and respiratory muscles (forced vital capacity)

- Tables 35 and 36 present the efficacy results from Study 1705 (data cutoff in October 2020), which is an open-label extension study of Study 1704, measured by the changes in the MG-ADL total score and QMG total score from baseline to Week 3 (the last dose of efgartigimod alfa) of each treatment cycle. The efficacy of efgartigimod alfa in patients with gMG was maintained during repeated treatment cycles.

The applicant's explanation about the differences in the efficacy and safety of efgartigimod alfa between Japanese and non-Japanese patients in Studies 1704 and 1705:

- Table 41 presents the percentages of MG-ADL responders, the primary endpoint, and the percentages of QMG responders, a key secondary endpoint, in the Japanese and non-Japanese subpopulations of Study 1704. The percentage of MG-ADL responders in the first treatment cycle in the anti-AChR antibody-positive subpopulation, the primary endpoint, tended to be higher in the efgartigimod alfa group than in the placebo group in the non-Japanese subpopulation, but tended to be higher in the placebo group than in the efgartigimod alfa group in the Japanese subpopulation. These tendencies were also observed in the overall population, which included both anti-AChR antibody-positive and -negative patients. The percentages of QMG responders in the first treatment cycle tended to be consistently higher in the efgartigimod alfa group than in the placebo group in the Japanese and non-Japanese subpopulations, both in the anti-AChR antibody-positive subpopulation and the overall population. The target sample size for Japanese patients in Study 1704 was 16. With this sample size determined based on the prior assumptions, the results from the Japanese subpopulation were expected to be consistent with those from the overall population with a probability of 83%.[48)]

Table 41. Percentages of MG-ADL responders and QMG responders in the first treatment cycle in the Japanese and non-Japanese subpopulations (Study 1704, mITT)

		Treatment	N	MG-ADL total score		QMG total score	
				MG-ADL responders	Percentage of MG-ADL responders	QMG responders	Percentage of QMG responders
Anti-AChR antibody-positive subpopulation	Japanese	Placebo	4	1	25.0% (1/4 patients)	0	0% (0/4 patients)
		Efgartigimod alfa	6	1	16.7% (1/6 patients)	1	16.7% (1/6 patients)
	Non-Japanese	Placebo	60	18	30.0% (18/60 patients)	9	15.0% (9/60 patients)
		Efgartigimod alfa	59	43	72.9% (43/59 patients)	40	67.8% (40/59 patients)
Overall population[a)]	Japanese	Placebo	7	3	42.9% (3/7 patients)	2	28.6% (2/7 patients)
		Efgartigimod alfa	8	3	37.5% (3/8 patients)	3	37.5% (3/8 patients)
	Non-Japanese	Placebo	76	28	36.8% (28/76 patients)	14	18.4% (14/76 patients)
		Efgartigimod alfa	76	54	71.1% (54/76 patients)	48	63.2% (48/76 patients)

a) The overall population included both anti-AChR antibody-positive and -negative patients.

- Table 42 presents the changes over time from baseline in MG-ADL total score during the first treatment cycle in individual Japanese patients. The percentage of patients achieving a ≥2-point decrease in MG-ADL total score, which was considered clinically significant improvement, during the study period was higher in the efgartigimod alfa group (87.5% [7 of 8 patients]) than in the placebo group (71.4% [5 of 7 patients]),

48) Simulated according to Method 2, a method for quantitatively assessing the probability of obtaining consistent results between the entire population and the Japanese population described in "Basic Principles of Global Clinical Trials" (PFSB/ELD Notification No. 0928010 dated September 28 2007). When the difference in the percentage of MG-ADL responders between the placebo group and the efgartigimod alfa group was taken as D, the between-treatment group difference in the overall population as D_{all}, and the between-treatment group difference in the Japanese subpopulation as D_{Japan}, the probability that $D_{Japan} > 0$ and $D_{all} > 0$ would occur, under the condition that a significant difference between the treatment groups was observed at a 2-sided significant level of 0.05 in the overall population.

with a tendency toward relatively prolonged ≥2-point decrease in MG-ADL total score in the efgartigimod alfa group as compared with the placebo group. Actually, the percentage (mean ± SE) of the duration of a ≥2-point decrease in MG-ADL total score in the study period (126 days) was higher in Japanese patients in the efgartigimod alfa group (48.2 ± 14.1%) than in the placebo group (37.1 ± 14.0%) in both the AChR antibody-positive subpopulation and the overall population including both AChR antibody-positive and -negative patients. A Japanese patient in the efgartigimod alfa group (Patient No. JPN0013234) was unable to visit at Weeks 5 and 6 and had missing MG-ADL total score data for the time points. The patient was therefore not identified as an MG-ADL responder despite achieving a ≥2-point decrease in MG-ADL total score at Week 4. Thus, the results of percentage of MG-ADL responders, the primary endpoint, failed to demonstrate evident efficacy of efgartigimod alfa in the Japanese subpopulation. However, taking into account the limited number of Japanese patients enrolled in the study, the missing MG-ADL total score data in 1 Japanese patient may have affected the efficacy evaluation in the Japanese subpopulation.

Table 42. Changes over time from baseline in MG-ADL total score during the first treatment cycle in individual Japanese patients (Study 1704)

Patient No.	Age[a] (years)	Autoantibodies[b]	Baseline	Change from baseline											
				Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 10	Week 12	Week 14	Week 16
Placebo															
JPN0001231	7[redacted]	AChR+	9	0	-1	-1	-1	-1	0	-1	-1		-1		
JPN0005119	5[redacted]	AChR+	6	0	-4	-5	-6	-4	-5	-4	-1	1			
JPN0005159	3[redacted]	AChR+	7	0	0	0	1	0	0	1	1	4			
JPN0009230	4[redacted]	AChR+	11	0	-2	-2	-4	-4	-1	-3	-6	-4	0		-4
JPN0004030	5[redacted]	AChR-/MuSK-	12	-4	-4	-7	-5	-5	-4	-5	-4	0			
JPN0005133	6[redacted]	AChR-/MuSK+	10	-3	-3	-4	-2	-2	-2	-2	-4	-3	-1	-3	-4
JPN0008112	5[redacted]	AChR-/MuSK-	9	0	0	0	0	-1	-1	-2	-1	0	0		
Efgartigimod alfa															
JPN0002209	4[redacted]	AChR+	6	-3	-1	-1	-1	-1	-1	-1	-2	-2	1	2	1
JPN0002232	6[redacted]	AChR+	9	-1	-1	0	-2	-1	-1	0	1	-1	0		
JPN0004025	4[redacted]	AChR+	5	0	1	1	2	2	2	1	1	1			
JPN0007101	5[redacted]	AChR+	13	0	-1	-1	-1	-1	-2	-1	0	0			
JPN0009233	6[redacted]	AChR+	10	0	-3	-3	-3	-3	-4		-5	-3	1		
JPN0013234	4[redacted]	AChR+	9	-5	-6	-6	-6			-6	-7	-6	-4	-2	-2
JPN0003089	7[redacted]	AChR-/MuSK-	13	-1	-5	-4	-2	-3	-4	-3	-2	-3	-7	-3	-3
JPN0007092	4[redacted]	AChR-/MuSK-	12	0	-4	-5	-5	-6	-6	-4	-5	-3	-3	-1	

a) At enrollment
b) AChR+, anti-AChR antibody-positive; AChR-, anti-AChR antibody-negative; MuSK+, anti-MuSK antibody-positive; MuSK-, anti-MuSK antibody-negative

- In the efgartigimod alfa group, baseline patient characteristics of Japanese anti-AChR antibody-positive patients were compared with non-Japanese anti-AChR antibody-positive patients. More Japanese patients (83.3% [5 of 6 patients]) were found to be under standard-of-care treatments for gMG with nonsteroidal immunosuppressants than non-Japanese patients (59.3% [35 of 59 patients]),[49] suggesting that more Japanese patients were receiving active therapeutic intervention at baseline. Further, the percentage of MG-ADL responders with a baseline MG-ADL total score of 5 to 7 points tended to be lower than that of MG-ADL responders with a baseline MG-ADL total score of ≥8 points [see Section 7.R.2.2], and the percentage of MG-ADL responders with a baseline MG-ADL total score of 5 to 7 points in the Japanese subpopulation (33.3% [2 of 6 patients]) was slightly higher than that in the non-Japanese subpopulation (23.7% [14 of 59 patients]).[50] Study 1704 enrolled extremely limited number of Japanese patients, which precluded precise assessment of how patient characteristics affect the efficacy evaluation in this subpopulation. Nevertheless, standard-of-care treatment used and baseline MG-ADL total score points were considered to have affected the efficacy evaluation to some extent.
- Tables 43 and 44 present the changes in MG-ADL total score and QMG total score, respectively, from baseline to Week 3 (the last dose of efgartigimod alfa) of each treatment cycle in the Japanese and non-Japanese subpopulations of Study 1705, an open-label, extension study of Study 1704 (data cutoff in

49) The percentages of anti-AChR antibody-positive patients who were on nonsteroidal immunosuppressants in the Japanese subpopulation were 75.0% (3 of 4 patients) in the placebo group and 83.3% (5 of 6 patients) in the efgartigimod alfa group, while those in the non-Japanese subpopulation were 56.7% (34 of 60 patients) and 59.3% (35 of 59 patients), respectively.

50) In the Japanese subpopulation, the baseline MG-ADL total scores in anti-AChR antibody-positive patients were 5 to 7 points in 50.0% (2 of 4) of patients in the placebo group and 33.3% (2 of 6) of patients in the efgartigimod alfa group, 8 to 9 points in 25.0% (1 of 4) of patients in the placebo group and 33.3% (2 of 6) of patients in the efgartigimod alfa group, and ≥10 points in 25.0% (1 of 4) of patients in the placebo group and 33.3% (2 of 6) of patients in the efgartigimod alfa group. In the non-Japanese subpopulation, the baseline MG-ADL total scores in anti-AChR antibody-positive patients were 5 to 7 points in 26.7% (16 of 60) of patients in the placebo group and 23.7% (14 of 59) of patients in the efgartigimod alfa group, 8 to 9 points in 46.7% (28 of 60) of patients in the placebo group and 39.0% (23 of 59) of patients in the efgartigimod alfa group, and ≥10 points in 26.7% (16 of 60) of patients in the placebo group and 37.3% (22 of 59) of patients in the efgartigimod alfa group.

February 2021). In the Japanese subpopulation, likewise in the non-Japanese subpopulation, the MG-ADL total score and QMG total score decreased, and the decreases were maintained during repeated treatment cycles.

Table 43. Changes in MG-ADL total score from baseline to Week 3 (the last dose of efgartigimod alfa) of each treatment cycle (Study 1705, overall population[a])

		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7
Japanese	Placebo/ efgartigimod alfa[b]	9.3 ± 1.45(3) 9.0 (7, 12)	8.7 ± 1.45(3) 9.0 (6, 11)	10.0 ± 1.53(3) 11.0 (7, 12)	9.7 ± 1.86(3) 11.0 (6, 12)	9.7 ± 1.45(3) 10.0 (7, 12)	9.0 ± 1.53(3) 10.0 (6, 11)	9, 11 (2) [c] 10.0 (9, 11)
		-2.7 ± 1.76(3) -2.0 (-6, 0)	-4.3 ± 0.88 (3) -4.0 (-6, -3)	-3.7 ± 1.45(3) -4.0 (-6, -1)	-4.7 ± 1.20(3) -4.0 (-7, -3)	-3.7 ± 1.45(3) -4.0 (-6, -1)	-3.0 ± 1.00(3) -2.0 (-5, -2)	-2.0, -2.0(2) [c] -2.0 (-2.0, -2.0)
	Efgartigimod alfa/ efgartigimod alfa[b]	9.7 ± 0.87(7) 9.0 (7, 13)	9.5 ± 1.06(6) 10.0 (6, 12)	10.3 ± 1.38(4) 10.5 (7, 13)	9.8 ± 1.31(4) 10.0 (7, 12)	7, 13 (2) [c] 10.0 (7, 13)	6, 13 (2) [c] 9.5 (6, 13)	7.0 (1) [c]
		-5.3 ± 0.99(7) -6.0 (-9, -1)	-4.3 ± 0.76(6) -4.0 (-7, -2)	-5.5 ± 1.55(4) -4.5 (-10, -3)	-4.7 ± 2.03(3) -5.0 (-8, -1)	-6, -3 (2) [c] -4.5 (-6, -3)	-3, -1 (2) [c] -2.0 (-3, -1)	-3.0 (1) [c]
Non-Japanese	Placebo/ efgartigimod alfa[b]	9.5 ± 0.38(63) 9.0 (5, 19)	9.8 ± 0.37(61) 9.0 (5, 18)	9.8 ± 0.42(54) 9.5 (5, 17)	10.1 ± 0.52 (42) 9.5 (5, 16)	10.3 ± 0.55(35) 11.0 (5, 16)	10.5 ± 0.59(33) 11.0 (5, 18)	10.8 ± 0.76(24) 10.0 (6, 18)
		-4.2 ± 0.43(62) -3.5 (-19, 1)	-4.5 ± 0.42(58) -4.0 (-13, 2)	-4.6 ± 0.47(53) -4.0 (-14, 1)	-4.5 ± 0.54 (41) -4.0 (-12, 0)	-5.1 ± 0.56(35) -5.0 (-14, 0)	-4.9 ± 0.62(30) -4.0 (-15, 1)	-5.9 ± 0.66(23) -5.0 (-15, -2)
	Efgartigimod alfa/ efgartigimod alfa[b]	10.4 ± 0.41(66) 10.0 (5, 18)	10.7 ± 0.45(60) 10.5 (5, 18)	10.9 ±0.51(51) 11.0 (5, 18)	11.0 ± 0.57(45) 11.0 (5, 19)	11.1 ± 0.61(39) 11.0 (5, 18)	10.7 ± 0.62(32) 10.0 (5, 17)	11.4 ± 0.63(25) 11.0 (6, 18)
		-6.2 ± 0.48(64) -6.0 (-16, 1)	-6.3 ± 0.53(58) -6.0 (-15, 1)	-6.7 ± 0.51(50) -7.0 (-15, 1)	-7.2 ± 0.58(44) -7.0 (-14, 1)	-7.2 ± 0.60(39) -7.0 (-14, 0)	-7.2 ± 0.74(29) -7.0 (-15, 1)	-7.8 ± 0.75 (22) -8.0 (-15, 0)

Mean ± SE (n), median (minimum, maximum)
Top, MG-ADL total score at baseline; bottom, the change in MG-ADL total score from baseline to Week 3 (the last dose of efgartigimod alfa)
a) The overall population included both anti-AChR antibody-positive and -negative patients.
b) The placebo/efgartigimod alfa group received placebo in Study 1704, and started to receive efgartigimod alfa in Cycle 1 of Study 1705. The efgartigimod alfa/efgartigimod alfa group had received efgartigimod alfa in Study 1704, but the table indicates treatment cycles in Study 1705 alone.
c) Individual values

Table 44. Changes in QMG total score from baseline to Week 3 (the last dose of efgartigimod alfa) of each treatment cycle (Study 1705, overall population[a])

		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7
Japanese	Placebo/ efgartigimod alfa[b]	12.3 ± 3.28(3) 14.0 (6, 17)	13.3 ± 2.33(3) 14.0 (9, 17)	12.7 ± 1.86(3) 14.0 (9, 15)	13.3 ± 3.18(3) 16.0 (7, 17)	13.3 ± 3.48(3) 14.0 (7, 19)	13.3 ± 2.91(3) 14.0 (8, 18)	13, 15 (2) [c] 14.0 (13, 15)
		-4.3 ± 1.33(3) -3.0 (-7. -3)	-5.7 ± 1.45(3) -6.0 (-8, -3)	-3.3 ± 0.33(3) -3.0 (-4, -3)	-4.0 ± 1.53(3) -5.0 (-6, -1)	-4.3 ± 2.33(3) -2.0 (-9, -2)	-5.7 ± 2.73(3) -4.0 (-11, -2)	1.0 (1) [c]
	Efgartigimod alfa/ efgartigimod alfa[b]	13.1 ± 2.50(7) 10.0 (6, 24)	12.7 ± 3.20(6) 9.0 (5, 24)	15.3 ± 4.89(4) 14.5 (6, 26)	15.5 ± 3.77(4) 15.0 (9, 23)	7, 20 (2) [c] 13.5 (7, 20)	2, 20 (2) [c] 11.0 (2, 20)	
		-3.8 ± 1.22(6) -3.5 (-9, -1)	-3.7 ± 1.20(6) -2.5 (-9, -1)	-4.8 ± 2.87(4) -4.5 (-12, 2)	-4, -2 (2) [c] -3 (-4, -2)	-4, -3 (2) [c] -3.5 (-4, -3)		
Non-Japanese	Placebo/ efgartigimod alfa[b]	16.6 ± 0.58(63) 17.0 (7, 26)	16.7 ± 0.61(61) 17.0 (8, 27)	16.1 ± 0.62(53) 16.0 (7, 25)	16.6 ± 0.95(37) 18.0 (1, 25)	17.1 ± 0.82(29) 17.0 (9, 25)	18.0 ± 0.95(27) 18.0 (8, 33)	18.8 ± 1.00(20) 19.5 (10, 28)
		-4.5 ± 0.45(61) -4.0 (-13, 3)	-4.2 ± 0.47(54) -3.5 (-13, 3)	-3.9 ± 0.62(48) -3.0 (-15, 3)	-3.2 ± 0.55(32) -3.0 (-9, 2)	-3.2 ± 0.63(25) -3.0 (-8, 2)	-4.4 ± 0.93(22) -4.0 (-17, 1)	-5.4 ± 0.98(15) -5.0 (-13, -1)
	Efgartigimod alfa/ efgartigimod alfa[b]	15.3 ± 0.77(66) 15.5 (1, 34)	16.1 ± 0.81(60) 16.0 (4, 34)	16.1 ± 0.87(48) 16.0 (0, 30)	14.5 ± 0.97(40) 14.0 (1, 30)	16.5 ± 1.22(28) 16.0 (5, 31)	14.6 ± 1.16(22) 15.0 (1, 29)	16.4 ± 1.42(15) 17.0 (5, 26)
		-5.2 ± 0.61(63) -5.0 (-19, 3)	-5.8 ± 0.60(53) -5.0 (-17, 2)	-6.0 ± 0.76(41) -5.0 (-18, 2)	-5.6 ± 0.91(30) -5.5 (-16, 3)	-5.9 ± 0.81(24) -5.0 (-13, -1)	-4.6 ± 1.18(15) -3.0 (-16, 3)	-5.7 ± 0.86(12) -5.5 (-12, -1)

Mean ± SE (n), median (minimum, maximum)
Top, QMG total score at baseline; bottom, the change in QMG total score from baseline to Week 3 (the last dose of efgartigimod alfa)
a) The overall population included both anti-AChR antibody-positive and -negative patients.
b) The placebo/efgartigimod alfa group received placebo in Study 1704, and started to receive efgartigimod alfa in Cycle 1 of Study 1705. The efgartigimod alfa/efgartigimod alfa group had received efgartigimod alfa in Study 1704, but the tables indicate treatment cycles in Study 1705 alone.
c) Individual values

- The pharmacodynamic effects of efgartigimod alfa in Study 1704, measured by the percent changes in the concentrations of total IgG and IgG subclasses from baseline to Week 4 (1 week after the last dose of efgartigimod alfa), did not differ substantially between the Japanese and non-Japanese subpopulations [Table 25].

- Table 45 shows the incidences of adverse events in the Japanese and non-Japanese subpopulations of Studies 1704 and 1705 (data cutoff in February 2021). In both studies, no Japanese patients receiving efgartigimod alfa experienced serious adverse events or adverse events leading to treatment discontinuation. In Study 1705, the incidence of nasopharyngitis tended to be higher in the Japanese subpopulation than in the non-Japanese subpopulation, but a causal relationship to the study drug was ruled out for all cases of nasopharyngitis. These study results indicated similarities in the types and frequencies of the adverse events reported in the Japanese and non-Japanese subpopulations, with no major safety concerns identified in the Japanese subpopulation.

Table 45. Incidences of adverse events in the Japanese and non-Japanese subpopulations (Studies 1704 and 1705)

	Study 1704						Study 1705[a)]		
	Overall population		Japanese		Non-Japanese		Overall population	Japanese	Non-Japanese
	Placebo	Efgartigimod alfa	Placebo	Efgartigimod alfa	Placebo	Efgartigimod alfa			
N	83	84	7	8	76	76	139	10	129
All adverse events	70 (84.3)	65 (77.4)	7 (100)	7 (87.5)	63 (82.9)	58 (76.3)	112 (80.6)	9 (90.0)	103 (79.8)
Deaths	0	0	0	0	0	0	5 (3.6)	0	5 (3.9)
Serious adverse events	7 (8.4)	4 (4.8)	2 (28.6)	0	5 (6.6)	4 (5.3)	21 (15.1)	0	21 (16.3)
Adverse events leading to drug discontinuation	3 (3.6)	3 (3.6)	1 (14.3)	0	2 (2.6)	3 (3.9)	8 (5.8)	0	8 (6.2)
Common adverse events									
Headache	23 (27.7)	24 (28.6)	0	2 (25.0)	23 (30.0)	22 (28.9)	31 (22.3)	1 (10.0)	30 (23.3)
Nasopharyngitis	15 (18.1)	10 (11.9)	4 (57.1)	2 (25.0)	11 (14.5)	8 (10.5)	15 (10.8)	4 (40.0)	11 (8.5)
Upper respiratory tract infection	4 (4.8)	9 (10.7)	0	0	4 (5.3)	9 (11.8)	5 (3.6)	0	5 (3.9)
Urinary tract infection	4 (4.8)	8 (9.5)	0	0	4 (5.3)	8 (10.5)	10 (7.2)	0	10 (7.8)
Nausea	9 (10.8)	7 (8.3)	0	0	9 (11.8)	7 (9.2)	7 (5.0)	1 (10.0)	6 (4.7)
Diarrhoea	9 (10.8)	6 (7.1)	1 (14.3)	1 (12.5)	8 (10.5)	5 (6.6)	12 (8.6)	2 (20.0)	10 (7.8)
Myalgia	1 (1.2)	5 (6.0)	0	1 (12.5)	1 (1.3)	4 (5.3)	4 (2.9)	2 (20.0)	2 (1.6)
Bronchitis	2 (2.4)	5 (6.0)	0	1 (12.5)	2 (2.6)	4 (5.3)	4 (2.9)	0	4 (3.1)
Oropharyngeal pain	7 (8.4)	3 (3.6)	0	0	7 (9.2)	3 (3.9)	7 (5.0)	0	7 (5.4)
Hypertension	6 (7.2)	3 (3.6)	0	0	6 (7.9)	3 (3.9)	5 (3.6)	0	5 (3.9)
Cough	5 (6.0)	3 (3.6)	0	1 (12.5)	5 (6.6)	2 (2.6)	3 (2.2)	0	3 (2.3)
Dizziness	5 (6.0)	3 (3.6)	0	0	5 (6.6)	3 (3.9)	6 (4.3)	1 (10.0)	5 (3.9)

n (incidence [%])
a) Totals for the placebo/efgartigimod alfa group and the efgartigimod alfa/efgartigimod alfa group

Based on the above investigation, the applicant explained that the efficacy and safety evaluation of efgartigimod alfa in Japanese patients with gMG based on the results from the overall population of Study 1704 was appropriate.

PMDA's view:

- The MG-ADL total score is used as a scale that measures the functional impairment associated with gMG, and selecting the percentage of MG-ADL responders, while taking into account individual disease variability, psychological factors, interrater variability, etc., as the primary endpoint for Study 1704 was largely acceptable. The percentage of MG-ADL responders in the anti-AChR antibody-positive subpopulation was statistically significantly higher in the efgartigimod alfa group than in the placebo group, successfully demonstrating the efficacy of efgartigimod alfa in anti-AChR antibody-positive patients

with gMG [for the efficacy of efgartigimod alfa by anti-AChR antibody status, see Section 7.R.2.1].

- Study 1704 failed to show consistency in the primary endpoint results between the Japanese subpopulation and the non-Japanese subpopulation. Nevertheless, individual Japanese patients receiving efgartigimod alfa achieved a ≥2-point decrease in MG-ADL total score, which was considered clinically significant improvement, and the duration of the ≥2-point decrease in MG-ADL total score tended to be longer in the efgartigimod alfa group than in the placebo group. In Study 1705, the changes in MG-ADL total score and QMG total score were similar in the Japanese and non-Japanese subpopulations. The percent changes in the concentrations of total IgG and IgG subclasses in Study 1704 were also similar in the Japanese and non-Japanese subpopulations. Based on these results, the efficacy evaluation of efgartigimod alfa in Japanese patients with gMG based on the results from the overall populations of Studies 1704 and 1705 is largely acceptable.
- Albeit in extremely small number of Japanese patients, Studies 1704 and 1705 suggested no safety concerns specific to this patient population.
- Accordingly, efficacy and safety evaluations of efgartigimod alfa in Japanese patients are feasible based on the results from the overall populations of Studies 1704 and 1705, the global studies of efgartigimod alfa. However, due to the limited experiences in the use of efgartigimod alfa in Japanese patients, safety and efficacy data of efgartigimod alfa should be further collected through post-marketing surveillance.
- The above PMDA's conclusions will be finalized taking into account comments from the Expert Discussion.

7.R.2 Efficacy

7.R.2.1 Efficacy by anti-AChR antibody status

PMDA asked the applicant to explain the efficacy of efgartigimod alfa by anti-AChR antibody status.

The applicant's explanation:

- Because foreign phase II study (CTD 5.3.5.1-1, Study 1602) evaluated the efficacy of efgartigimod alfa targeting in anti-AChR antibody-positive patients, no data were obtained from anti-AChR antibody-negative patients receiving efgartigimod alfa. Therefore, the global phase III study (CTD 5.3.5.1-2, Study 1704) included both anti-AChR antibody-positive and -negative patients, while its primary endpoint was defined as the percentage of MG-ADL responders in the first treatment cycle in the anti-AChR antibody-positive patients and the percentage of MG-ADL responders in the overall population, including anti-AChR antibody-positive and -negative patients as the secondary endpoint. An adjustment was made for multiplicity arising from testing of the primary and secondary endpoints, and type I error was controlled by using a hierarchical testing procedure.
- Table 46 presents the percentages of MG-ADL responders (the primary endpoint) and QMG responders (a secondary endpoint) by anti-AChR antibody status in Study 1704. Although the percentage of MG-ADL responders in the anti-AChR antibody-positive subpopulation tended to be higher in the efgartigimod alfa group than in the placebo group, the percentage of MG-ADL responders in the anti-AChR antibody-negative subpopulation did not differ substantially between the treatment groups. In contrast, the percentage of QMG responders tended to be higher in the efgartigimod alfa group than in the placebo group in both the anti-AChR antibody-positive and -negative subpopulations.

Table 46. Percentages of MG-ADL responders and QMG responders during the first treatment cycle by anti-AChR antibody status (Study 1704, mITT)

	Treatment	N	MG-ADL total score		QMG total score	
			MG-ADL responders	Percentage of MG-ADL responders	QMG responders	Percentage of QMG responders
Anti-AChR antibody-positive	Placebo	64	19	29.7% (19/64 patients)	9	14.1% (9/64 patients)
	Efgartigimod alfa	65	44	67.7% (44/65 patients)	41	63.1% (41/65 patients)
Anti-AChR antibody-negative	Placebo	19	12	63.2% (12/19 patients)	7	36.8% (7/19 patients)
	Efgartigimod alfa	19	13	68.4% (13/19 patients)	10	52.6% (10/19 patients)

- Although the cause of the higher percentage of MG-ADL responders in the placebo group than in the efgartigimod alfa group in the anti-AChR antibody-negative subpopulations remained unclear due to the limited number of patients, the percentages of MG-ADL responders (29.7% and 63.2%, respectively) were higher than the percentages of QMG responders (14.1% and 36.8%, respectively) in the placebo group of both the anti-AChR antibody-positive and -negative subpopulations, suggesting that the MG-ADL total score, a patient-reported outcome measure, was likely to be more sensitive to placebo response than the QMG total score, which was a physician-rated outcome measure based on quantitative test results. The MG-ADL total score was therefore considered to be largely affected by placebo response, particularly in the anti-AChR antibody-negative subpopulation, which was small in number.
- Table 47 presents the changes in MG-ADL total score and QMG total score from baseline to Week 4 (1 week after the last dose of the study drug), by anti-AChR antibody status in Study 1704. In both the anti-AChR antibody-positive and -negative subpopulations, the changes in the scores tended to be great in the efgartigimod alfa group as compared with the placebo group.

Table 47. Changes in MG-ADL total score and QMG total score during the first treatment cycle by anti-AChR antibody status (Study 1704, mITT)

		Placebo			Efgartigimod alfa		
		Baseline	Week 4	Change	Baseline	Week 4	Change
MG-ADL total score	Anti-AChR antibody-positive	8.6 ± 0.27 (64) 8.0 (5, 16)	6.7 ± 0.39 (60) 7.0 (0, 15)	-1.8 ± 0.31 (60) -1.0 (-8, 4)	9.0 ± 0.31 (65) 9.0 (5, 15)	4.4 ± 0.44 (63) 4.0 (0, 14)	-4.6 ± 0.40 (63) -5.0 (-11, 2)
	Anti-AChR antibody-negative	9.8 ± 0.58 (19) 10.0 (6, 14)	7.1 ± 0.85 (19) 8.0 (1, 13)	-2.7 ± 0.54 (19) -2.0 (-7, 1)	9.7 ± 0.72 (19) 8.0 (6, 17)	5.4 ± 0.84 (17) 5.0 (0, 12)	-4.2 ± 0.82 (17) -4.0 (-13, 0)
QMG total score	Anti-AChR antibody-positive	15.2 ± 0.56 (62) 15.5 (6, 24)	14.5 ± 0.62 (60) 15.0 (1, 22)	-1.0 ± 0.37 (58) -1.0 (-8, 7)	16.0 ± 0.64 (65) 16.0 (4, 28)	9.7 ± 0.68 (62) 8.5 (0, 28)	-6.2 ± 0.66 (62) -5.5 (-17, 3)
	Anti-AChR antibody-negative	16.5 ± 1.19 (19) 16.0 (8, 27)	12.3 ± 1.44 (19) 11.0 (3, 25)	-4.2 ± 1.42 (19) -3.0 (-18, 6)	16.6 ± 1.06 (19) 17.0 (8, 25)	10.3 ± 1.38 (17) 8.0 (3, 19)	-6.1 ± 1.04 (17) -5.0 (-13, -1)

Top, mean ± SE (n); bottom, median (minimum, maximum)

- The efficacy of efgartigimod alfa based on MG-ADL subscores and QMG subscores in Study 1704 was analyzed by anti-AChR antibody status. Tables 48 and 49 present the changes in MG-ADL subscores and QMG subscores, respectively, from baseline to Week 4 (1 week after the last dose of the study drug) of the first treatment cycle. The changes in most of both MG-ADL subscores and QMG subscores were greater in the efgartigimod alfa group than in the placebo group, indicating a tendency toward improved individual MG symptoms by treatment with efgartigimod alfa in both anti-AChR antibody-positive and -negative subpopulations.

Table 48. Changes in MG-ADL subscores during the first treatment cycle by anti-AChR antibody status (Study 1704, mITT)

	Subscore[a)]	Placebo			Efgartigimod alfa		
		Baseline	Week 4	Change	Baseline	Week 4	Change
Anti-AChR antibody-positive	Ocular muscles	2.0 ± 0.16 (64) 2.0 (0, 4)	1.9 ± 0.20 (60) 2.0 (0, 6)	-0.1 ± 0.15 (60) 0.0 (-3, 4)	2.4 ± 0.18 (65) 2.0 (0, 6)	1.6 ± 0.20 (63) 1.0 (0, 5)	-0.7 ± 0.15 (63) -1.0 (-5, 2)
	Gross motor or limb impairment	2.6 ± 0.15 (64) 3.0 (0, 5)	2.0 ± 0.18 (60) 2.0 (0, 4)	-0.7 ± 0.15 (60) 0.0 (-3, 2)	2.6 ± 0.15 (65) 3.0 (0, 5)	1.2 ± 0.16 (63) 1.0 (0, 4)	-1.4 ± 0.16 (63) -1.0 (-4, 1)
	Respiratory muscles	1.1 ± 0.07 (64) 1.0 (0, 2)	1.0 ± 0.08 (60) 1.0 (0, 2)	-0.1 ± 0.07 (60) 0.0 (-2, 1)	1.0 ± 0.07 (65) 1.0 (0, 2)	0.6 ± 0.08 (63) 1.0 (0, 2)	-0.4 ± 0.09 (63) 0.0 (-2, 1)
	Bulbar symptoms	2.9 ± 0.14 (64) 3.0 (1, 6)	2.0 ± 0.19 (60) 2.0 (0, 6)	-0.9 ± 0.14 (60) -1.0 (-5, 1)	3.1 ± 0.17 (65) 3.0 (0, 6)	1.0 ± 0.17 (63) 1.0 (0, 5)	-2.1 ± 0.21 (63) -2.0 (-5, 3)
Anti-AChR antibody-negative	Ocular muscles	3.1 ± 0.40 (19) 3.0 (0, 6)	2.4 ± 0.42 (19) 2.0 (0, 6)	-0.6 ± 0.27 (19) 0.0 (-3, 1)	3.0 ± 0.47 (19) 3.0 (0, 6)	1.8 ± 0.44 (17) 1.0 (0, 6)	-1.1 ± 0.35 (17) 0.0 (-5, 0)
	Gross motor or limb impairment	2.8 ± 0.32 (19) 3.0 (0, 5)	2.2 ± 0.33 (19) 2.0 (0, 5)	-0.6 ±0.26 (19) -1.0 (-4, 1)	2.6 ± 0.21 (19) 3.0 (1, 4)	1.5 ± 0.26 (17) 2.0 (0, 3)	-1.2 ± 0.23 (17) -1.0 (-3, 0)
	Respiratory muscles	1.1 ± 0.14 (19) 1.0 (0, 2)	0.7 ± 0.15 (19) 1.0 (0, 2)	-0.3 ± 0.15 (19) 0.0 (-2, 1)	1.1 ± 0.13 (19) 1.0 (0, 2)	0.7 ± 0.14 (17) 1.0 (0, 2)	-0.5 ± 0.15 (17) 0.0 (-2, 0)
	Bulbar symptoms	2.8 ± 0.28 (19) 3.0 (1, 5)	1.7 ± 0.30 (19) 2.0 (0, 5)	-1.1 ± 0.26 (19) -1.0 (-4, 0)	3.0 ± 0.35 (19) 3.0 (1, 6)	1.4 ± 0.30 (17) 1.0 (0, 4)	-1.5 ± 0.39 (17) -1.0 (-5, 1)

Top, mean ± SE (n); bottom, median (minimum, maximum)

a) Ocular muscles (double vision, eyelid ptosis), bulbar symptoms (talking, chewing, swallowing), respiratory muscles (breathing), and gross motor or limb impairment (impairment of ability to brush teeth or comb hair, impairment of ability to arise from a chair)

Table 49. Changes in QMG subscores during the first treatment cycle by anti-AChR antibody status (Study 1704, mITT)

	Subscore[a)]	Placebo			Efgartigimod alfa		
		Baseline	Week 4	Change	Baseline	Week 4	Change
Anti-AChR antibody-positive	Ocular muscles	2.4 ± 0.20 (62) 2.0 (0, 6)	2.4 ± 0.21 (60) 3.0 (0, 6)	0.0 ± 0.15 (58) 0.0 (-2, 4)	2.6 ± 0.23 (65) 3.0 (0, 6)	1.6 ± 0.21 (62) 1.0 (0, 6)	-1.0 ± 0.21 (62) -1.0 (-6, 3)
	Facial muscles	1.1 ± 0.10 (62) 1.0 (0, 3)	1.0 ± 0.10 (60) 1.0 (0, 3)	-0.2 ± 0.08 (58) 0.0 (-2, 1)	1.2 ± 0.11 (65) 1.0 (0, 3)	0.6 ± 0.08 (62) 1.0 (0, 2)	-0.7 ± 0.11 (62) 0.0 (-3, 1)
	Bulbar symptoms	1.2 ± 0.15 (62) 1.0 (0, 4)	0.8 ± 0.14 (60) 0.0 (0, 4)	-0.5 ± 0.13 (58) 0.0 (-3, 1)	1.7 ± 0.16 (65) 2.0 (0, 5)	0.4 ± 0.08 (62) 0.0 (0, 3)	-1.3 ± 0.16 (62) -1.0 (-4, 1)
	Gross motor	8.2 ± 0.33 (62) 9.0 (3, 14)	8.2 ± 0.36 (60) 9.5 (0, 12)	-0.2 ± 0.22 (58) 0.0 (-4, 4)	8.4 ± 0.34 (65) 9.0 (1, 14)	5.9 ± 0.43 (62) 5.5 (0, 14)	-2.5 ± 0.36 (62) -2.0 (-9, 2)
	Axial muscles	1.7 ± 0.08 (62) 2.0 (0, 3)	1.6 ± 0.08 (60) 2.0 (0, 3)	-0.2 ± 0.06 (58) 0.0 (-1, 1)	1.6 ± 0.08 (65) 2.0 (0, 3)	1.0 ± 0.10 (62) 1.0 (0, 3)	-0.6 ± 0.09 (62) -1.0 (-2, 1)
	Respiratory muscles	0.6 ± 0.11 (62) 0.0 (0, 3)	0.6 ± 0.11 (60) 0.0 (0, 3)	0.1 ± 0.09 (58) 0.1 (-2, 2)	0.5 ± 0.10 (65) 0.0 (0, 3)	0.3 ± 0.08 (62) 0.0 (0, 2)	-0.1 ± 0.08 (62) 0.0 (-2, 1)
Anti-AChR antibody-negative	Ocular muscles	3.2 ± 0.44 (19) 3.0 (0, 6)	2.5 ± 0.43 (19) 3.0 (0, 6)	-0.7 ± 0.43 (19) 0.0 (-6, 2)	3.3 ± 0.50 (19) 3.0 (0, 6)	2.2 ± 0.54 (17) 1.0 (0, 6)	-0.9 ± 0.46 (17) 0.0 (-5, 3)
	Facial muscles	0.9 ± 0.16 (19) 1.0 (0, 2)	0.7 ± 0.17 (19) 1.0 (0, 2)	-0.2 ± 0.12 (19) 0.0 (-1, 1)	1.1 ± 0.15 (19) 1.0 (0, 3)	0.5 ± 0.17 (17) 0.0 (0, 2)	-0.6 ± 0.19 (17) 0.0 (-3, 0)
	Bulbar symptoms	1.4 ± 0.27 (19) 1.0 (0, 4)	1.1 ± 0.29 (19) 1.0 (0, 3)	-0.3 ± 0.32 (19) 0.0 (-3, 2)	1.1 ± 0.24 (19) 1.0 (0, 3)	0.4 ± 0.17 (17) 0.0 (0, 2)	-0.7 ± 0.27 (17) 0.0 (-3, 1)
	Gross motor	8.9 ± 0.66 (19) 10.0 (4, 14)	6.5 ± 0.85 (19) 6.0 (2, 14)	-2.4 ± 0.71 (19) -2.0 (-10, 3)	8.9 ± 0.44 (19) 9.0 (4, 12)	5.9 ± 0.73 (17) 6.0 (1, 10)	-2.9 ± 0.62 (17) -3.0 (-7, 0)
	Axial muscles	1.6 ± 0.14 (19) 2.0 (0, 2)	1.1 ± 0.16 (19) 1.0 (0, 2)	-0.5 ± 0.19 (19) -1.0 (-2, 1)	1.8 ± 0.14 (19) 2.0 (1, 3)	1.1 ± 0.15 (17) 1.0 (0, 2)	-0.8 ± 0.16 (17) -1.0 (-2, 0)
	Respiratory muscles	0.5 ± 0.19 (19) 0.0 (0, 3)	0.4 ± 0.16 (19) 0.0 (0, 2)	-0.1 ± 0.12 (19) 0.0 (-2, 1)	0.4 ± 0.18 (19) 0.0 (0, 2)	0.1 ± 0.08 (17) 0.0 (0, 1)	-0.1 ± 0.08 (17) 0.0 (-1, 0)

Top, mean ± SE (n); bottom, median (minimum, maximum)

a) Ocular muscles (double vision, eyelid ptosis), facial muscles (facial muscle strength), bulbar symptoms (swallowing of 4 oz. of water, and speech after counting aloud from 1 to 50), gross motor (right and left hand grip, arm outstretched, and leg outstretched), axial muscles (head lifted), and respiratory muscles (forced vital capacity)

- The efficacy of efgartigimod alfa administered in repeated treatment cycles was evaluated in the global long-term extension study (CTD 5.3.5.2-2, Study 1705) (data cutoff in February 2021). Tables 50 and 51 present the changes in MG-ADL total score and QMG total score, respectively from baseline to Week 3 (the last dose of efgartigimod alfa) of each treatment cycle by anti-AChR antibody status. In both anti-AChR antibody-positive and -negative subpopulations, MG-ADL total score and QMG total score decreased and the decreases were maintained, with no substantial difference in the efficacy of efgartigimod alfa according to anti-AChR antibody status.

Table 50. Changes in MG-ADL total score from baseline to Week 3 (the last dose of efgartigimod alfa) of each treatment cycle by anti-AChR-antibody status (Study 1705)

		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7
Anti-AChR antibody-positive	Placebo/ efgartigimod alfa[a)]	9.0 ± 0.37(48) 9.0 (5, 16)	9.2 ± 0.38(47) 9.0 (5, 17)	9.3 ± 0.45(41) 9.0 (5, 17)	9.9 ± 0.60(33) 9.0 (5, 16)	9.9 ± 0.63(27) 9.0 (5, 15)	9.9 ± 0.66(26) 9.5 (5, 18)	10.5 ± 0.95(17) 10.0 (6, 18)
		-4.0 ± 0.41(47) -3.0 (-10, 1)	-4.4 ± 0.43(44) -4.0 (-9, 2)	-4.3 ± 0.49(41) -4.0 (-12, 1)	-4.7 ± 0.58(32) -4.0 (-12, 0)	-4.6 ± 0.57(27) -4.0 (-11, 0)	-4.7 ± 0.74(23) -4.0 (-15, 1)	-5.5 ± 0.84(16) -4.0 (-15, -2)
	Efgartigimod alfa/ efgartigimod alfa[a)]	10.2 ± 0.43(58) 10.0 (5, 18)	10.3 ± 0.48(52) 10.0 (5, 18)	10.8 ± 0.55(45) 11.0 (5, 18)	10.7 ± 0.58(41) 11.0 (5, 19)	10.9 ± 0.65(34) 11.0 (5, 18)	10.7 ± 0.67(29) 10.0 (5, 17)	11.4 ± 0.68(22) 11.0 (6, 18)
		-6.0 ± 0.49(56) -6.0 (-16,1)	-6.2 ± 0.55(51) -6.0 (-15,1)	-6.4 ± 0.52(44) -6.0 (-13, 1)	-7.0 ± 0.62(39) -7.0 (-13, 1)	-7.1 ± 0.61(34) -7.0 (-14, 0)	-7.0 ± 0.80(26) -7.0 (-15, 1)	-8.1 ± 0.73(19) -8.0 (-15, -2)
Anti-AChR antibody-negative	Placebo/ efgartigimod alfa[a)]	10.7 ± 0.87(18) 10.5 (5, 19)	11.1 ± 0.79(17) 11.0 (7, 18)	11.1 ± 0.77(16) 11.0 (6, 17)	10.7 ± 0.86(12) 11.5 (6, 16)	11.3 ± 0.84(11) 12.0 (6, 16)	11.4 ± 1.00(10) 11.0 (5, 16)	11.1 ± 0.99(9) 11.0 (6, 16)
		-4.5 ± 1.06(18) -3.5 (-19, 0)	-4.8 ± 0.94(17) -4.0 (-13, 0)	-5.3 ± 1.01(15) -4.0 (-14, 0)	-4.3 ± 1.07(12) -3.0 (-12, 0)	-6.0 ± 1.15(11) -6.0 (-14, -1)	-5.0 ± 0.86(10) -4.5 (-10, -2)	-5.7 ± 1.03(9) -6.0 (-11, -2)
	Efgartigimod alfa/ efgartigimod alfa[a)]	11.0 ± 0.80(15) 11.0 (5, 16)	11.4 ± 0.86(14) 11.0 (6, 18)	11.4 ± 1.00(10) 11.5 (6, 17)	12.0 ± 1.30(8) 11.5 (6, 18)	11.9 ± 1.40(7) 13.0 (6, 17)	9.8 ± 1.46(5) 9.0 (6, 15)	10.3 ± 1.89(4) 10.0 (6, 15)
		-6.4 ± 1.06(15) -8.0 (-15, -1)	-5.5 ± 1.07(13) -5.0 (-12, 0)	-7.3 ± 1.31(10) -8.0 (-15, -1)	-7.1 ± 1.46(8) -6.5 (-14, -2)	-7.0 ± 1.79(7) -5.0 (-14, -1)	-6.0 ± 2.02(5) -5.0 (-11, 0)	-5.3 ± 2.50(4) -4.5 (-12, 0)

Mean ± SE (n), median (minimum, maximum)

Top, MG-ADL total score at baseline; bottom, the change in MG-ADL total score from baseline to Week 3 (the last dose of efgartigimod alfa)

a) The placebo/efgartigimod alfa group received placebo in Study 1704, and started to receive efgartigimod alfa in Cycle 1 of Study 1705. The efgartigimod alfa/efgartigimod alfa group had received efgartigimod alfa in Study 1704, but the table indicates treatment cycles in Study 1705 alone.

Table 51. Changes in QMG total score from baseline to Week 3 (the last dose of efgartigimod alfa) of each treatment cycle by anti-AChR-antibody status (Study 1705)

		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7
Anti-AChR antibody-positive	Placebo/ efgartigimod alfa[a)]	15.9 ± 0.65(48) 16.5 (6, 25)	16.4 ± 0.71(47) 16.0 (8, 27)	15.6 ± 0.76(40) 15.5(7, 25)	16.4 ± 1.01(29) 16.0 (6, 25)	16.4 ± 1.01(24) 16.5 (7, 24)	17.1 ± 1.09(23) 17.0 (8, 33)	18.7 ± 1.12(15) 18.0 (12, 28)
		-4.2 ± 0.52(46) -3.0 (-13, 3)	-4.8 ± 0.52(41) -4.0 (-13, 0)	-3.5 ± 0.66(37) -3.0 (-15, 3)	-3.2 ± 0.64(27) -3.0 (-9, 2)	-3.0 ± 0.70(21) -2.0 (-8, 2)	-4.5 ± 1.03(19) -4.0 (-17, 1)	-5.1 ± 1.16(11) -4.0 (-13, -1)
	Efgartigimod alfa/ efgartigimod alfa[a)]	15.3 ± 0.84(58) 15.0 (4, 34)	15.9 ± 0.91(52) 16.0 (4, 34)	16.0 ± 0.98(43) 16.0 (0, 30)	14.5 ± 1.01(36) 14.0 (1, 30)	16.8 ± 1.37(25) 16.0 (5, 31)	14.5 ± 1.36(21) 15.0 (1, 29)	17.1 ± 1.45(13) 17.0 (5, 26)
		-5.1 ± 0.62(54) -4.5 (-16, 3)	-5.7 ± 0.65(48) -5.0 (-17, 2)	-5.4 ± 0.82(36) -4.5 (-18, 2)	-5.3 ± 0.93(28) -4.5 (-16, 3)	-5.7 ± 0.82(23) -4.0 (-13, -1)	-4.7 ± 1.35(13) -3.0 (-16, 3)	-5.9 ± 0.91(11) -6.0 (-12, -1)
Anti-AChR antibody-negative	Placebo/ efgartigimod alfa[a)]	17.6 ± 1.23(18) 17.0 (7, 26)	17.0 ± 1.14(17) 17.0 (9, 26)	16.7 ± 0.89(16) 16.0 (10, 24)	16.4 ± 2.03(11) 18.0 (1, 22)	17.8 ± 1.24(8) 17.5 (14, 25)	19.0 ± 1.72(7) 19.0 (13, 25)	17.7 ± 1.92(7) 19.0 (10, 23)
		-5.3 ± 0.78(18) -5.5 (-12, -1)	-2.9 ± 0.88(16) -3.0 (-9, 3)	-4.9 ± 1.24(14) -4.0 (-15, 3)	-3.4 ± 0.73(8) -3.5 (-6, -1)	-4.0 ± 1.21(7) -4.0 (-9, 0)	-4.8 ± 1.70(6) -4.0 (-11, -1)	-4.8 ± 2.18(5) -5.0 (-12, 1)
	Efgartigimod alfa/ efgartigimod alfa[a)]	14.3 ± 1.56(15) 15.0 (1, 24)	15.4 ± 1.68(14) 16.0 (4, 24)	16.0 ± 1.90(9) 16.0 (7, 26)	15.3 ± 2.51(8) 16.0 (4, 23)	14.2 ± 1.83(5) 16.0 (7, 17)	12.7 ± 1.86(3) 14.0 (9, 15)	7, 17 (2)[b)] 12.0 (7, 17)
		-4.9 ± 1.37(15) -3.0 (-19, 1)	-5.0 ± 1.07(11) -5.0 (-11, 2)	-7.8 ± 1.51(9) -8.0 (-13, -1)	-6.5 ± 2.33(4) -5.5 (-13, -2)	-6.0 ± 2.52(3) -4.0 (-11, -3)	-6, -2 (2)[b)] -4.0 (-6, -2)	-3.0 (1)[b)]

Efgartigimod alfa/efgartigimod alfa[a)]Mean ± SE (n), median (minimum, maximum)

Top, QMG total score at baseline; bottom, the change in QMG total score from baseline to Week 3 (the last dose of efgartigimod alfa)

a) The placebo/efgartigimod alfa group received placebo in Study 1704, and started to receive efgartigimod alfa in Cycle 1 of Study 1705. The efgartigimod alfa/efgartigimod alfa group had received efgartigimod alfa in Study 1704, but the table indicates treatment cycles in Study 1705 alone.

b) Individual values

- Table 52 presents changes from baseline in MG-ADL total score during the first treatment cycle in anti-MuSK antibody-positive patients (3 each in the placebo group and the efgartigimod alfa group) in the anti-AChR antibody-negative subpopulation (19 each in the placebo group and the efgartigimod alfa group) of Study 1704. All these patients were identified as MG-ADL responders. Due to the extremely small number of anti-MuSK antibody-positive patients, no substantial difference in the efficacy measured by MG-ADL total score was identified between the placebo group and the efgartigimod alfa group. In contrast, the change from baseline in total IgG concentration, in anti-MuSK antibody-positive patients was greater in the efgartigimod alfa group than in the placebo group, suggesting a tendency toward declining total IgG concentration via treatment with efgartigimod alfa [Table 23]. In light of the action mechanism of efgartigimod alfa, efgartigimod alfa is expected to have efficacy in anti-MuSK antibody-positive patients

as well.

Table 52. Changes from baseline in MG-ADL total score during the first treatment cycle in anti-MuSK antibody-positive patients (Study 1704)

Patient No.	Age[a] (years)	Autoantibodies[b]	Baseline	Change											
				Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 10	Week 12	Week 14	Week 16
Placebo															
GEO0003127	3[redacted]	AChR-/MuSK+	8	-2	-2	-3	-5	-5	-5	-6	-7	-5	-4	-4	-4
JPN0005133	6[redacted]	AChR-/MuSK+	10	-3	-3	-4	-2	-2	-2	-2	-4	-3	-1	-3	-4
SRB0001134	3[redacted]	AChR-/MuSK+	7	-2	-4	-4	-4	-4	-4	0	-2	-1			
Efgartigimod alfa															
CZE0005079	5[redacted]	AChR-/MuSK+	6	0	0	-1	-2	-2	-3	-4	-2	-3	-1		
SRB0001131	5[redacted]	AChR-/MuSK+	8	0	1	0	-4	-2	-5	-5	-5	-4	-5	-6	-6
USA0006035	4[redacted]	AChR-/MuSK+	6	-4	-6	-6	-6	-6	-6	-6	-6	-4	5		

a) At enrollment
b) AChR-, anti-AChR antibody-negative; MuSK+, anti-MuSK antibody-positive

- In anti-AChR antibody-positive patients or anti-AChR antibody-negative and anti-MuSK antibody-positive patients, the expression of IgG autoantibodies is thought to the direct cause of the pathological condition of gMG. Also in anti-LRP4 antibody-positive patients with double-seronegative (anti-AChR antibody-negative and anti-MuSK antibody-negative) gMG, the expression of IgG autoantibodies has been suggested to be the cause of its pathological condition [see Section 3.R.1]. Plasmapheresis for IgG removal has been reported to be effective against gMG in both anti-AChR antibody-positive and -negative patients, regardless of the type of autoantibodies (*Clin Exp Neuroimmunol.* 2015;6:21-31). The clinical study results showed that efgartigimod alfa decreased the concentrations of total IgG [Table 23] and all IgG subclasses [Table 26], both in the anti-AChR antibody-positive and -negative subpopulations, suggesting promising efficacy of efgartigimod alfa in both anti-AChR antibody-positive and -negative patients.
- As described above, albeit no substantial difference in the percentage of MG-ADL responders between the placebo group and the efgartigimod alfa group in the anti-AChR antibody-negative subpopulation, the results of Study 1704 demonstrated the efficacy of efgartigimod alfa by QMG responder percentage in the anti-AChR antibody-negative subpopulation as well. In addition, results from Studies 1704 and 1705 showed that the changes from baseline in MG-ADL total score and QMG total score did not differ substantially between the anti-AChR antibody-positive and -negative subpopulations, and that total IgG concentration decreased in both subpopulations. All these results demonstrated the efficacy of efgartigimod alfa in anti-AChR antibody-negative patients as well.

PMDA's view:

- The percentage of MG-ADL responders during the first treatment cycle in the anti-AChR antibody-positive subpopulation, the primary endpoint in Study 1704, was statistically significantly higher in the efgartigimod alfa group than in the placebo group [Table 33]. The efficacy of efgartigimod alfa in patients with anti-AChR antibody-positive gMG has thus been demonstrated.
- In contrast, in the anti-AChR antibody-negative subpopulation of Study 1704, the percentage of MG-ADL responders was higher in the placebo group than in the efgartigimod alfa group, showing no substantial difference between the treatment groups [Table 46]. The limited number of anti-AChR antibody-negative

patients hindered the clarification of the cause of the higher percentage of MG-ADL responders in the placebo group than in the efgartigimod alfa group. Nevertheless, the applicant has explained that the possible high placebo response in the MG-ADL total score, owing to being a patient-reported measure, could have been a cause of the higher responder percentage in the placebo group, which is considered acceptable.

- In the anti-AChR antibody-negative subpopulation of Study 1704, the percentage of QMG responders tended to be higher in the efgartigimod alfa group than in the placebo group [Table 46]. In addition, in Study 1704 and its extension study, Study 1705, the changes from baseline in MG-ADL total score and QMG total score decreased after the start of treatment with efgartigimod alfa in both anti-AChR antibody-positive and -negative subpopulations, with no substantial differences between the subpopulations [Tables 47 to 51].
- The anti-AChR antibody-negative subpopulation included anti-MuSK antibody-positive patients, anti-LRP4 antibody-positive and double seronegative (i.e., anti-AChR antibody-negative and anti-MuSK antibody-negative) patients, etc. (a) The expression of IgG autoantibodies has been suggested as the cause of the pathological condition of gMG in these patients; (b) treatment with efgartigimod alfa has been shown to decrease the concentrations of IgG subclasses, including pathogenic IgG autoantibodies; and, (c) the benefits of plasmapheresis have been proven in anti-AChR antibody-negative patients. In view of these observations, the applicant explains that efgartigimod alfa has promising efficacy in anti-AChR antibody-negative patients including anti-MuSK antibody-positive patients, which is understandable.
- Despite the limited number of anti-AChR antibody-negative patients evaluated, the safety evaluation by anti-AChR antibody status in Study 1704 and its extension study, Study 1705, identified no safety concerns specific to anti-AChR antibody-negative patients [see Section 7.R.3.1].
- As discussed above, efgartigimod alfa may be intended not only for anti-AChR antibody-positive patients but also for anti-AChR antibody-negative patients.
- The above PMDA's conclusions will be finalized taking into account the comments from the Expert Discussion.

7.R.2.2 Factors that may affect the efficacy of efgartigimod alfa

PMDA asked the applicant to explain the factors that may affect the efficacy of efgartigimod alfa.

The applicant's explanation:

- Table 53 presents the results of subgroup analyses for the percentages of MG-ADL responders and QMG responders by patient characteristics in the global phase III study (CTD 5.3.5.1-2, Study 1704). The percentages of MG-ADL responders and QMG responders were high in the efgartigimod alfa group as compared with the placebo group, demonstrating the efficacy of efgartigimod alfa regardless of patient characteristics.
- In the subgroup with a baseline MG-ADL total score of 5 to 7 points, the difference in the percentage of MG-ADL responders between the placebo group and the efgartigimod alfa group tended to be smaller than in the subgroup with a baseline MG-ADL total score of ≥8 points, while the between-group difference in the percentage of QMG responders did not differ substantially according to QMG total score at baseline.

- In patients with prior thymectomy, the difference in the percentage of MG-ADL responders between the placebo group and the efgartigimod alfa group was smaller than in those without prior thymectomy. However, the between-group difference in the percentage of QMG responders did not differ substantially according to prior thymectomy.
- Subgroup analyses for the percentages of MG-ADL responders and QMG responders by concomitant standard-of-care treatments for gMG showed no substantial differences between the placebo group and the efgartigimod alfa group.

Table 53. Percentages of MG-ADL responders and QMG responders in the first treatment cycle by patient characteristics (Study 1704, mITT, overall population[a])

		MG-ADL responders			QMG responders		
		Placebo	Efgartigimod alfa	Between-group difference [95% CI]	Placebo	Efgartigimod alfa	Between-group difference [95% CI]
Gender	Male	28.6 (8/28)	61.9 (13/21)	33.3 [6.7, 60.0]	10.7 (3/28)	76.2 (16/21)	65.5 [44.0, 87.0]
	Female	41.8 (23/55)	69.8 (44/63)	28.0 [10.7, 45.3]	23.6 (13/55)	55.6 (35/63)	31.9 [15.3, 48.6]
Age	<65 years	43.5 (30/69)	67.1 (49/73)	23.6 [7.7, 39.5]	20.3 (14/69)	58.9 (43/73)	38.6 [23.9, 53.4]
	≥65 years	7.1 (1/14)	72.7 (8/11)	65.6 [36.0, 95.2]	14.3 (2/14)	72.7 (8/11)	58.4 [26.4, 90.5]
Age[b]	<45 years	45.9 (17/37)	72.5 (29/40)	26.6 [5.4,47.8]	10.8 (4/37)	65.0 (26/40)	54.2 [36.3, 72.0]
	≥45 years	30.4 (14/46)	63.6 (28/44)	33.2 [13.7,52.7]	26.1 (12/46)	56.8 (25/44)	30.7 [11.4, 50.1]
Body weight[b]	<74 kg	46.3 (19/41)	63.2 (24/38)	16.8 [-4.8,38.5]	19.5 (8/41)	52.6 (20/38)	33.1 [13.1, 53.1]
	≥74 kg	28.6 (12/42)	71.7 (33/46)	43.2 [24.3,62.0]	19.0 (8/42)	67.4 (31/46)	48.3 [30.3, 66.4]
Age at diagnosis[b]	<36 years	40.0 (16/40)	70.2 (33/47)	30.2 [10.2,50.2]	10.0 (4/40)	61.7 (29/47)	51.7 [35.0, 68.4]
	≥36 years	34.9 (15/43)	64.9 (24/37)	30.0 [9.0,50.9]	27.9 (12/43)	59.5 (22/37)	31.6 [10.8, 52.3]
Duration of gMG[b]	<7 years	38.1 (16/42)	79.5 (31/39)	41.4 [22.0,60.8]	16.7 (7/42)	69.2 (27/39)	52.6 [34.2, 70.9]
	≥7 years	36.6 (15/41)	57.8 (26/45)	21.2 [0.6,41.8]	22.0 (9/41)	53.3 (24/45)	31.4 [12.1, 50.7]
MG-ADL total score at baseline	5 to 7 points	40.9 (9/22)	55.0 (11/20)	14.1 [-15.9, 44.0]	22.7 (5/22)	55.0 (11/20)	32.3 [4.3, 60.2]
	8 to 9 points	29.4 (10/34)	71.0 (22/31)	41.6 [19.4, 63.7]	17.6 (6/34)	74.2 (23/31)	56.5 [36.5, 76.6]
	≥10 points	44.4 (12/27)	72.7 (24/33)	28.3 [4.2, 52.4]	18.5 (5/27)	51.5 (17/33)	33.0 [10.5, 55.5]
Prior thymectomy	Present	30.6 (11/36)	61.0 (36/59)	30.5 [10.9,50.0]	8.3 (3/36)	55.9 (33/59)	47.6 [32.0, 63.2]
	Absent	42.6 (20/47)	84.0 (21/25)	41.4 [21.3,61.6]	27.7 (13/47)	72.0 (18/25)	44.3 [22.6, 66.1]
Concomitant corticosteroids	Any	35.8 (24/67)	63.3 (38/60)	27.5 [10.8,44.3]	20.9 (14/67)	65.0 (39/60)	44.1 [28.6, 59.6]
	None	43.8 (7/16)	79.2 (19/24)	35.4 [6.2,64.7]	12.5 (2/16)	50.0 (12/24)	37.5 [11.8, 63.2]
Concomitant non steroidal immunosuppressants	Any	39.2 (20/51)	64.7 (33/51)	25.5 [6.7,44.2]	11.8 (6/51)	56.9 (29/51)	45.1 [28.9, 61.3]
	None	34.4 (11/32)	72.7 (24/33)	38.4 [16.0,60.8]	31.1 (10/32)	66.7 (22/33)	35.4 [12.7, 58.1]
Concomitant cholinesterase inhibitors	Any	32.8 (22/67)	69.0 (49/71)	36.2 [20.6,51.7]	14.9 (10/67)	60.6 (43/71)	45.6 [31.4, 59.9]
	None	56.3 (9/16)	61.5 (8/13)	5.3 [-30.6,41.2]	37.5 (6/16)	61.5 (8/13)	24.0 [-11.5, 59.6]

Percentage of responders (n/N)
a) The overall population included both anti-AChR antibody-positive and -negative patients.
b) Stratified by the median

As described above, the subgroup analyses identified no factors that substantially affect the efficacy of efgartigimod alfa. Therefore, the efficacy of efgartigimod alfa is expected regardless of patient characteristics.

PMDA accepted the applicant's explanation.

7.R.3 Safety

7.R.3.1 Safety of efgartigimod alfa

PMDA asked the applicant to explain the safety of efgartigimod alfa, based on the results of the global phase III study (CTD 5.3.5.1-2, Study 1704) and the global long-term extension study (CTD 5.3.5.2-2, Study 1705).

The applicant's explanation:

- Table 45 presents the incidences of common adverse events reported in Study 1704 and Study 1705 (data cutoff in February 2021).
- In Study 1704, there were no tendencies toward increasing incidences of adverse events, serious adverse events, or adverse events leading to drug discontinuation in the efgartigimod alfa group as compared with the placebo group. Serious adverse events were reported in 7 patients in the placebo group and 4 patients in the efgartigimod alfa group. A causal relationship to the study drug was ruled out in most of these patients including those in the placebo group, except for 1 patient in the efgartigimod alfa group (thrombocytosis).
- In Study 1705 (data cutoff in February 2021), 5 patients (3.6%) died from adverse events (septic shock, acute myocardial infarction, myasthenia gravis crisis, lung neoplasm malignant, and death in 1 patient each). A causal relationship to the study drug was ruled out for all deaths. Serious adverse events were reported in 15.1% (21 of 139) of patients, and a causal relationship to the study drug was ruled out for all events. Table 54 presents the incidences of adverse events during each treatment cycle of Study 1705. There were no tendencies toward increasing incidences of adverse events with increasing number of cycles.

Table 54. Incidences of adverse events during each treatment cycle in Study 1705 (Study 1705,[a)] safety analysis set)

	Total	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8	Cycle 9
N	139	139	130	112	94	79	70	52	38	17
All adverse events	112 (80.6)	72 (51.8)	58 (44.6)	36 (32.1)	31 (33.0)	24 (30.4)	24 (34.3)	13 (25.0)	8 (21.1)	3 (17.6)
Serious adverse events	21 (15.1)	7 (5.0)	6 (4.6)	3 (2.7)	4 (4.3)	1 (1.3)	4 (5.7)	1 (1.9)	0	0
Adverse events leading to drug discontinuation	8 (5.8)	1 (0.7)	2 (1.5)	1 (0.9)	3 (3.2)	0	1 (1.4)	0	0	0

n (incidence [%])
a) The sum of the placebo/efgartigimod alfa group and the efgartigimod alfa/efgartigimod alfa group

PMDA asked the applicant to explain the safety of efgartigimod alfa by anti-AChR antibody status.

The applicant's explanation:

Table 55 presents the incidences of adverse events by anti-AChR antibody status in Study 1704 and Study 1705 (data cutoff in February 2021). Despite the small number of anti-AChR antibody-negative patients as compared with anti-AChR antibody-positive patients that precluded strict comparisons, the safety profiles of efgartigimod alfa did not differ substantially regardless of anti-AChR antibody status.

Table 55. Incidences of adverse events by anti-AChR antibody status (Studies 1704 and 1705, safety analysis sets)

	Study 1704				Study 1705[a)]	
	Anti-AChR antibody-positive		Anti-AChR antibody-negative		Anti-AChR antibody-positive	Anti-AChR antibody-negative
	Placebo	Efgartigimod alfa	Placebo	Efgartigimod alfa		
N	64	65	19	19	106	33
All adverse events	54 (84.4)	49 (75.4)	16 (84.2)	16 (84.2)	81 (76.4)	31 (93.9)
Serious adverse events	6 (9.4)	3 (4.6)	1 (5.3)	1 (5.3)	18 (17.0)	3 (9.1)
Adverse events leading to drug discontinuation	3 (4.7)	2 (3.1)	0	1 (5.3)	6 (5.7)	2 (6.1)
Common adverse events						
Headache	17 (26.6)	17 (26.2)	6 (31.6)	7 (36.8)	22 (20.8)	9 (27.3)
Nasopharyngitis	11 (17.2)	9 (13.8)	4 (21.1)	1 (5.3)	11 (10.4)	4 (12.1)
Upper respiratory tract infection	2 (3.1)	9 (13.8)	2 (10.5)	0	4 (3.8)	1 (3.0)
Nausea	6 (9.4)	5 (7.7)	3 (15.8)	2 (10.5)	6 (5.7)	1 (3.0)
Diarrhoea	8 (12.5)	5 (7.7)	1 (5.3)	1 (5.3)	10 (9.4)	2 (6.1)
Urinary tract infection	3 (4.7)	5 (7.7)	1 (5.3)	3 (15.8)	8 (7.5)	2 (6.1)
Bronchitis	1 (1.6)	3 (4.6)	1 (5.3)	2 (10.5)	3 (2.8)	1 (3.0)
Back pain	1 (1.6)	3 (4.6)	3 (15.8)	1 (5.3)	5 (4.7)	0
Hypertension	4 (6.3)	3 (4.6)	2 (10.5)	0	4 (3.8)	1 (3.0)
Oropharyngeal pain	4 (6.3)	2 (3.1)	3 (15.8)	1 (5.3)	5 (4.7)	2 (6.1)
Procedural headache	0	2 (3.1)	1 (5.3)	2 (10.5)	1 (0.9)	2 (6.1)
Vomiting	0	1 (1.5)	2 (10.5)	1 (5.3)	4 (3.8)	2 (6.1)
Contusion	1 (1.6)	1 (1.5)	1 (5.3)	2 (10.5)	0	2 (6.1)
Pain	0	0	0	2 (10.5)	1 (0.9)	1 (3.0)
Ear infection	0	0	0	2 (10.5)	0	0
Neck pain	1 (1.6)	0	0	2 (10.5)	0	1 (3.0)

n (incidence [%])
a) The sum of the placebo/efgartigimod alfa group and the efgartigimod alfa/efgartigimod alfa group

PMDA accepted the applicant's explanation. Based on the submitted clinical study results on the safety of efgartigimod alfa, the safety risks associated with the use of efgartigimod alfa are considered acceptable. However, due to the limited use of efgartigimod alfa in Japanese patients including anti-AChR antibody-negative patients, safety information needs to be further collected in the post-marketing setting.

PMDA's above conclusion will be finalized taking into account the comments from the Expert Discussion.

Infection-related adverse events and infusion-related reactions are further discussed in the following sections [see Sections 7.R.3.2 and 7.R.3.3].

7.R.3.2 Infection-related adverse events

Efgartigimod alfa's effect to lower IgG concentration may affect immune functions. PMDA asked the applicant to explain the occurrence of infections in patients receiving efgartigimod alfa.

The applicant's explanation:

Table 56 presents the incidences of infection-related adverse events[51)] in the global phase III study (CTD

51) Events coded under the MedDRA SOC "Infections and infestations"

5.3.5.1-2, Study 1704) and the global long-term extension study (CTD 5.3.5.2-2, Study 1705) (data cutoff in February 2021).

- In Study 1704, the incidence of infection-related adverse events was higher in the efgartigimod alfa group (46.4% [39 of 84 patients]) than in the placebo group (37.3% [31 of 83 patients]). The infection-related adverse events reported with a higher incidence in the efgartigimod alfa group than in the placebo group were upper respiratory tract infection, urinary tract infection, and bronchitis. A causal relationship to the study drug was ruled out for all these events in both treatment groups. A serious infection-related adverse event was reported in 1 patient in the placebo group (upper respiratory tract infection). There were no reports of opportunistic infection in Study 1704.
- In Study 1705, the incidence of infection-related adverse events was 46.8% (65 of 139 patients). Infection-related adverse events reported by ≥3 patients were nasopharyngitis (15 patients), urinary tract infection (10 patients), COVID-19 (6 patients), herpes zoster and upper respiratory tract infection (5 patients each), bronchitis (4 patients), and oral herpes, respiratory tract infection, and cystitis (3 patients each). A causal relationship to the study drug could not be ruled out for herpes zoster in 3 patients and bronchitis, oral herpes, and cystitis in 1 patient each. Serious infection-related adverse events were reported in 6 patients (COVID-19 pneumonia in 2, and septic shock, urinary tract infection, pneumonia escherichia, dysentery, COVID-19, and pneumonia in 1 each [including patients reporting ≥2 events]). A causal relationship to the study drug was ruled out for all events. There were no reports of opportunistic infection in Study 1705.

Table 56. Incidences of infection-related adverse events (Studies 1704 and 1705, safety analysis sets)

	Study 1704		Study 1705[a)]
	Placebo	Efgartigimod alfa	
N	83	84	139
All adverse events	31 (37.3)	39 (46.4)	65 (46.8)
Serious adverse events	1 (1.2)	0	6 (4.3)
Adverse events leading to drug discontinuation	0	0	2 (1.4)
Common adverse events			
Nasopharyngitis	15 (18.1)	10 (11.9)	15 (10.8)
Upper respiratory tract infection	4 (4.8)	9 (10.7)	5 (3.6)
Urinary tract infection	4 (4.8)	8 (9.5)	10 (7.2)
Bronchitis	2 (2.4)	5 (6.0)	4 (2.9)
Influenza	3 (3.6)	3 (3.6)	2 (1.4)
Ear infection	0	2 (2.4)	0
Sinusitis	0	2 (2.4)	1 (0.7)
Cystitis	2 (2.4)	0	3 (2.2)
COVID-19	0	0	6 (4.3)
Herpes zoster	0	0	5 (3.6)
Oral herpes	0	1 (1.2)	3 (2.2)
Respiratory tract infection	1 (1.2)	0	3 (2.2)

n (incidence [%])
a) The sum of the placebo/efgartigimod alfa group and the efgartigimod alfa/efgartigimod alfa group

- The trough total IgG concentrations observed in patients who received efgartigimod alfa in the foreign phase II study (CTD 5.3.5.1-1, Study 1602), Study 1704, and Study 1705 (data cutoff in October 2020) were divided into quartile groups (≤25 percentile, >25 percentile to ≤50 percentile, >50 percentile to ≤75 percentile, and >75 percentile) to assess the relationship with the incidences of infection-related adverse

events. Table 57 presents the assessment results. The incidences of infection-related adverse events tended to be higher in patients with a trough total IgG concentration below the median (2.52 g/L), which included the groups of "≤25 percentile" (53.7% [22 of 41 patients]) and ">25 percentile to ≤50 percentile" (59.0% [23 of 39 patients]), than in those with a trough total IgG concentration above the median (2.52 g/L), which included the groups of ">50 percentile to ≤75 percentile" (48.7% [19 of 39 patients]) and ">75 percentile" (46.2% [18 of 39 patients]).

Table 57. Incidences of infection-related infections by quartiles of trough total IgG concentration (patients receiving efgartigimod alfa in Studies 1602, 1704, and 1705)

	≤25 percentile[b)]	>25 percentile to ≤50 percentile[c)]	>50 percentile to ≤75 percentile[d)]	>75 percentile
N[a)]	41	39	39	39
All adverse events	22 (53.7)	23 (59.0)	19 (48.7)	18 (46.2)
Serious adverse events	1 (2.4)	2 (5.1)	3 (7.7)	0
Adverse events leading to drug discontinuation	0	1 (2.6)	0	0
Common adverse events				
Nasopharyngitis	6 (14.6)	2 (5.1)	7 (17.9)	7 (17.9)
Upper respiratory tract infection	5 (12.2)	4 (10.3)	3 (7.7)	0
Urinary tract infection	3 (7.3)	4 (10.3)	2 (5.1)	4 (10.3)
Cystitis	3 (7.3)	0	0	0
Bronchitis	2 (4.9)	3 (7.7)	0	2 (5.1)
Herpes zoster	2 (4.9)	2 (5.1)	0	1 (2.6)
Pharyngitis	2 (4.9)	1 (2.6)	0	1 (2.6)
Pneumonia	2 (4.9)	0	0	1 (2.6)
Gastroenteritis	1 (2.4)	0	0	2 (5.1)
Oral herpes	1 (2.4)	1 (2.6)	2 (5.1)	0
Influenza	0	4 (10.3)	0	1 (2.6)
Gingivitis	0	2 (5.1)	0	0
Respiratory tract infection	0	0	3 (7.7)	0
COVID-19	0	0	2 (5.1)	0

n (incidence [%]) The quartiles of trough total IgG concentration were based on the results as of the data cutoff in April 2020, and the incidences of infection-related adverse events were based on the results as of the data cutoff in October 2020.
a) Of the 162 patients, 4 had no tough total IgG concentration data and were therefore not included in the table.
b) Total IgG concentration (25th percentile), 2.01 g/L; c) Total IgG concentration (50th percentile), 2.52 g/L
d) Total IgG concentration (75th percentile), 3.25 g/L

- There is no established threshold guidelines for total IgG concentrations levels that require close monitoring (*JAMA Netw Open.* 2018;1:e184169). Nevertheless, patients with total IgG concentration decreasing to <3 g/L following rituximab treatment were reported to have an increased risk of infections and frequently undergo immunoglobulin replacement therapy (*Front Immunol.* 2021;12:671503). Given this, the incidences of infection-related adverse events were analyzed using a cutoff total IgG concentration of 3 g/L. A total of 150 patients who received efgartigimod alfa in Study 1704 and Study 1705 (data cutoff in February 2021) were divided into 2 groups: one with a trough total IgG concentration of "<3 g/L" and the other with a concentration of "≥3 g/L" during each treatment cycle. The incidence of infection-related adverse events in the "<3 g/L" group (60.7% [65 of 107 patients]) tended to be higher than that in the "≥3 g/L" group (48.8% [21 of 43 patients]). The incidences of serious infection-related adverse events were 5.6% (6 of 107 patients) in the "<3 g/L" group and 0% (0 of 43 patients) in the "≥3 g/L" group, and those of infection-related adverse events leading to drug discontinuation were 1.9% (2 of 107 patients) and 0% (0 of 43 patients), respectively. Thus, serious infection-related adverse events and infection-related adverse

events leading to drug discontinuation occurred solely in patients with a trough total IgG concentration of <3 g/L.[52)]

- In the 150 patients receiving efgartigimod alfa in Study 1704 and Study 1705 (data cutoff in February 2021), the incidences of infection-related adverse events were analyzed according to the use of concomitant corticosteroids or nonsteroidal immunosuppressants for gMG. Infection-related adverse events were reported in 56.5% (65 of 115) of patients receiving corticosteroids, 60.0% (21 of 35) of patients receiving no corticosteroids, 62.6% (57 of 91) of patients receiving nonsteroidal immunosuppressants, 49.2% (29 of 59) of patients receiving no nonsteroidal immunosuppressants, 62.8% (49 of 78) of patients receiving both corticosteroids and nonsteroidal immunosuppressants, and 51.4% (37 of 72) of patients receiving neither corticosteroids nor nonsteroidal immunosuppressants. Thus, patients receiving both corticosteroids and nonsteroidal immunosuppressants showed a slightly higher incidence of infection-related adverse events than those receiving neither of the drugs. However, the incidence of serious adverse events, including but not limited to infections, did not differ substantially according to the concomitant use of corticosteroids or nonsteroidal immunosuppressants, with no clinically relevant differences shown according to the use of concomitant medications.
- When administered in cycles, efgartigimod alfa, a human IgG antibody Fc fragment, transiently decreases IgG concentration. However, efgartigimod alfa does not affect the concentrations of other immunoglobulins (IgA, IgD, IgE, and IgM) or albumin and is unlikely to have direct effects on B-cells. The risk of infections associated with efgartigimod alfa is thus unlikely to pose a clinically relevant problem.
- Nevertheless, the possible increased risk of infections through the transient decrease in IgG concentration by efgartigimod alfa should be taken into account. The package insert will provide a cautionary note on the potential increase in the risk of infections during treatment with efgartigimod alfa along with advice on the use of efgartigimod alfa in patients with complications of infection.

PMDA asked the applicant to explain the safety of efgartigimod alfa, when administered to patients presenting with myasthenia gravis crisis (MG crisis).

The applicant's explanation:

- MG crisis is characterized by worsened respiratory and bulbar muscle weakness in patients with gMG, causing respiratory failure and requiring mechanical ventilation with endotracheal intubation. Patients presenting with MG crisis need hospitalization due to unstable disease conditions. Therefore, endotracheally intubated patients in MGFA Classification Clinical Class V were excluded from the foreign phase II study (CTD 5.3.5.1-1, Study 1602), Studies 1704 and 1705, in which efgartigimod alfa was administered in the outpatient setting. Accordingly, there are no clinical study results on the safety of efgartigimod alfa administered to patients presenting with MG crisis.
- In Study 1705 (data cutoff in February 2021), 2 patients experienced MG crisis. Because both patients developed pneumonia at the onset of MG crisis, the possibility could not be denied that pneumonia had induced MG crisis. However, one of them presented with MG crisis 55 days after the last dose of

[52)] The trough total IgG concentrations in 6 patients experiencing serious infection-related adverse events (including 2 patients who discontinued study treatment due to infection-related adverse events) ranged from 1.98 to 2.65 g/L.

efgartigimod alfa, and the causative organism of pneumonia was found to be *Escherichia coli*, which is characteristic of pneumonia aspiration and ventilator-associated pneumonia. The other patient developed MG crisis after the second dose of efgartigimod alfa in the second treatment cycle, which did not coincide with the trough total IgG concentration. Accordingly, a causal relationship between MG crisis and efgartigimod alfa was later ruled out in both patients. Although the most common contributing factor to MG crisis is infection (*Neurohospitalist.* 2011;1:16-22), there has been no evidence that treatment with efgartigimod alfa increases the risk of serious infections, suggesting that efgartigimod alfa is unlikely to cause or worsen MG crisis.

- Accordingly, albeit no systematic investigation, no particular safety concerns have been identified up to the present. The provision of particular cautionary advice through the package insert will be unnecessary on the use of efgartigimod alfa in patients presenting with MG crisis. Nevertheless, the use of efgartigimod alfa should be discontinued in patients presenting with infections or those who require IVIg or hemocatharsis for MG crisis. IVIg or hemocatharsis warrants attention to potential drug interactions with efgartigimod alfa in view of its therapeutic effects [see Section 6.R.4]. Nevertheless, these procedures may be performed immediately after the discontinuation of efgartigimod alfa upon the onset of MG crisis, depending on the patient's condition.

PMDA's view:

- In Study 1704, the efgartigimod alfa group showed high incidences of infection-related adverse events as compared with the placebo group, and the efgartigimod alfa group tended to show high incidences of upper respiratory tract infection and urinary tract infection, etc.
- The assessment of the incidences of infection-related adverse events by quartiles of trough total IgG concentration in patients receiving efgartigimod alfa in Studies 1602, 1704, and 1705 revealed that the incidences of infection-related adverse events tended to be high in patients with a trough IgG concentration below the median (2.52 g/L) as compared with those with the concentration above the median [Table 57]. Also in patients receiving efgartigimod alfa in Studies 1704 and 1705, patients with a trough total IgG concentration of <3.0 g/L tended to show high incidences of infection-related adverse events as compared with those with a concentration of ≥3.0 g/L, and tended to carry an increased risk of serious infections.
- Given these results, treatment with efgartigimod alfa may induce or worsen infections through decreased IgG concentrations, warranting attention to the onset of MG crisis associated with infections.
- Therefore, the package insert should provide cautionary advice on the need for close observation of the patient's condition, including appropriate IgG concentration monitoring. In addition, post-marketing data should be collected to elucidate the relationship between decreased IgG concentrations during treatment with efgartigimod alfa and the risk of infections.

7.R.3.3 Infusion-related reactions

PMDA asked the applicant to explain the occurrence of infusion-related reactions during treatment with efgartigimod alfa.

The applicant's explanation:

Table 58 presents the incidences of infusion-related reactions[53)] in the global phase III study (CTD 5.3.5.1-2, Study 1704) and the global long-term extension study (CTD 5.3.5.2-2, Study 1705) (data cutoff in February 2021).

- In Study 1704, the incidences of infusion-related reactions were low in the efgartigimod alfa group (3.6% [3 of 84 patients]) as compared with the placebo group (9.6% [8 of 83 patients]), with no serious adverse events, adverse events leading to drug discontinuation, or moderate or severe adverse events reported in either treatment groups.
- In Study 1705, the most common infusion-related reaction was rash reported in 3 patients. A causal relationship to the study drug could not be ruled out in all these patients. No serious infusion-related reactions or infusion-related reactions leading to drug discontinuation were reported, and most of the infusion-related reactions were mild, except for moderate rash in 1 patient.
- Neither anaphylaxis nor anaphylactoid shock was reported in Studies 1704 or 1705.
- The protocols of Studies 1704 and 1705 had no particular prescriptions for prophylaxis (e.g., corticosteroids, antihistamines, and/or antipyretic analgesics) against infusion-related reactions. In Study 1705, 1 patient presented with rash during the first treatment cycle and received an antihistamine prior to the administration of efgartigimod alfa in subsequent treatment cycles. However, no other patients were pretreated to reduce infusion-related reactions.

Table 58. Incidences of infusion-related reactions (Studies 1704 and 1705, safety analysis sets)

	Study 1704		Study 1705[a)]
	Placebo	Efgartigimod alfa	
N	83	84	139
All adverse events	8 (9.6)	3 (3.6)	10 (7.2)
Serious adverse events	0	0	0
Adverse events leading to drug discontinuation	0	0	0
Common adverse events			
Pruritus	1 (1.2)	1 (1.2)	0
Swelling of eyelid	0	1 (1.2)	0
Rash macular	0	1 (1.2)	0
Infusion site extravasation	1 (1.2)	0	0
Injection site pain	1 (1.2)	0	0
Cough	1 (1.2)	0	2 (1.4)
Dyspnoea	1 (1.2)	0	1 (0.7)
Erythema	1 (1.2)	0	0
Rash	1 (1.2)	0	3 (2.2)
Rash erythematous	1 (1.2)	0	0
Rash maculo-papular	1 (1.2)	0	2 (1.4)
Sensation of foreign body	0	0	1 (0.7)
Dermatitis	0	0	1 (0.7)

n (incidence [%])

a) The sum of the placebo/efgartigimod alfa group and the efgartigimod alfa/efgartigimod alfa group

- Based on these outcomes, the risk of infusion-related reactions associated with the infusion of efgartigimod alfa is unlikely to pose a clinically relevant problem. Nevertheless, likewise other biological products, the package insert of efgartigimod alfa will provide a cautionary note that patients should be closely monitored

53) Events coded under the broad category of a standardized MedDRA query (SMQ) "Hypersensitivity," "Anaphylactic Reaction," or "Extravasation events (excluding implants)," which occurred within 48 hours of study drug administration or within 2 days of study drug administration for patient with unknown exact dosing start time

for possible infusion-related reactions during treatment with efgartigimod alfa; and if any abnormalities are found, treatment with efgartigimod alfa should be discontinued and appropriate measures should be taken.

PMDA accepted the applicant's explanation. However, infusion-related reactions are likely to occur in association with the infusion of efgartigimod alfa as observed with other biological products, and only a limited number of patients were enrolled in the clinical studies of efgartigimod alfa. Relevant data should be further collected in the post-marketing setting.

7.R.4 Clinical positioning

PMDA asked the applicant to explain the clinical positioning of efgartigimod alfa in the treatment of gMG.

The applicant's explanation:

- Currently, the Japanese gMG treatment guidelines (*Japanese Clinical Guidelines for Myasthenia Gravis 2014*. Nankodo Co., Ltd., 2014) recommends immunotherapy as standard treatment, along with the supportive use of cholinesterase inhibitors. Immunotherapy for gMG begins with low-dose corticosteroids or nonsteroidal immunosuppressants (cyclosporine or tacrolimus hydrate), and cholinesterase inhibitors (e.g., pyridostigmine bromide and ambenonium) are supportively used depending on the disease conditions. Other options for patients who do not adequately respond to these treatments and require an immediate improvement of symptoms include IVIg, hemocatharsis (e.g., plasma exchange and immunoadsorption), and high-dose intravenous corticosteroids (steroid pulse therapy) (*Japanese Clinical Guidelines for Myasthenia Gravis 2014*. Nankodo Co., Ltd., 2014; *Neurol. Therap*. 2020;37:421-4).
- Oral corticosteroids, which induce adverse drug reactions such as weight increased, hypertension, diabetes mellitus, osteoporosis, and gastrointestinal disorders, are recommended to be used at low doses in a long term. High-dose intravenous corticosteroid therapy (steroid pulse therapy) requires special caution because it causes transient exacerbation in the early stage (*Japanese Clinical Guidelines for Myasthenia Gravis 2014*. Nankodo Co., Ltd., 2014). Nonsteroidal immunosuppressants are characterized by a delayed onset of effects (*Neurol Int Open.* 2018;2:E84-E92), different magnitude of the effects among individuals, and adverse drug reactions such as infection risk, diabetes mellitus, renal impairment, and hepatic function disorders.
- For patients who do not adequately respond to oral corticosteroids or nonsteroidal immunosuppressants and require immediate recovery from exacerbated symptoms, IVIg or hemocatharsis (e.g., plasma exchange and immunoadsorption) is selected. However, IVIg and hemocatharsis have only transient effects, requiring treatments on a regular basis for the long-term control of symptoms, which would be physically burdensome for patients. Hemocatharsis is particularly invasive and available at only limited medical facilities.
- Eculizumab is used in patients with anti-AChR antibody-positive gMG only when the symptoms are uncontrollable by IVIg or hemocatharsis (*Neurology.* 2016;87:419-25; *Lancet Neurol.* 2017;16:947-8). However, caution should be exercised against the risk of adverse drug reactions such as serious infections (meningococcal infections).
- Thymectomy is a recommended treatment option to be considered for patients with anti-AChR antibody-positive gMG complicated by thymoma (*Neurol. Therap.* 2020;37:421-4).

- Despite such conventional treatments, approximately 10% to 15% of patients with gMG fail to respond to the treatments. Patients with refractory gMG suffer from persistent symptoms (*Yale J Biol Med.* 2013;86:255-60; *J Clin Neuromuscul Dis.* 2014;15:167-78).
- Efgartigimod alfa is an FcRn-targeted human IgG1 antibody Fc fragment with modified amino acid residues. With its action mechanism different from the conventional gMG drugs, efgartigimod alfa inhibits FcRn-mediated IgG recycling and decreases the concentrations of IgG antibodies including pathogenic IgG autoantibodies, thereby exerting its effect against gMG. Efgartigimod alfa has no clinically relevant impacts on immunoglobulins other than IgG (i.e., IgA, IgD, IgE, and IgM) or serum albumin [see Section 3.R.1].
- The results of the global phase III study (CTD 5.3.5.1-2, Study 1704) and the global long-term extension study (CTD 5.3.5.2-2, Study 1705) demonstrated the efficacy and safety of efgartigimod alfa in patients with anti-AChR antibody-positive or -negative gMG who had been on stable doses of the standard-of-care treatments (cholinesterase inhibitors, corticosteroids, and/or nonsteroidal immunosuppressants) for their primary disease (gMG) [see Sections 7.R.2 and 7.R.3]. In the clinical studies, patients discontinued treatment with efgartigimod alfa if they required rescue therapy with IVIg or hemocatharsis. In light of possible drug interactions with efgartigimod alfa [see Section 6.R.4], the concurrent use of IVIg or hemocatharsis with efgartigimod alfa is not intended.
- Accordingly, efgartigimod alfa is expected to offer a new treatment option to patients with gMG and is expected to be used before IVIg or hemocatharsis that may be mainly chosen for tentative treatment of exacerbated gMG symptoms.

PMDA's view:

In view of the efgartigimod alfa's action mechanism different from conventional gMG drugs' and based on the submitted clinical study results, etc., efgartigimod alfa will offer a new treatment option for gMG, the applicant's explanation is thus acceptable. However, the clinical positioning of efgartigimod alfa is to be concluded taking into account the comments from the Expert Discussion. The appropriateness of the indication of efgartigimod alfa in view of on its clinical positioning is further discussed in Section 7.R.5.

7.R.5 Indication

PMDA asked the applicant to explain the appropriateness of the proposed indication of efgartigimod alfa in view of its clinical positioning.

The applicant's explanation:

- The global phase III study (CTD 5.3.5.1-2, Study 1704) and the global long-term extension study (CTD 5.3.5.2-2, Study 1705) targeted patients who were on stable doses of the standard-of-care treatments (cholinesterase inhibitors, corticosteroids, and/or nonsteroidal immunosuppressants) for their primary disease (gMG) and demonstrated the efficacy and safety of efgartigimod alfa administered in addition to their standard-of-care treatments [see Sections 7.R.2 and 7.R.3]. The inclusion criteria of these studies did not clearly require patients to have been on particular gMG treatments or inadequately responsive to the treatments. Therefore the studies did not target only patients with non-refractory gMG. In Study 1704 excluded patients who received IVIg or hemocatharsis within 1 month prior to screening and those who

received eculizumab within 6 months prior to the first dose of the study drug, and those who underwent rescue therapy with IVIg or hemocatharsis during treatment with efgartigimod alfa were required to discontinue the treatment.

- In Japan, the clinical guidelines for MG (*Japanese Clinical Guidelines for Myasthenia Gravis 2014*. Nankodo Co., Ltd., 2014) recommends immunotherapy as standard gMG treatment, with the supportive use of cholinesterase inhibitors.
- The percentages of MG-ADL responders and QMG responders in Study 1704 by the concomitant use of each standard-of-care treatment for the primary disease (gMG) (cholinesterase inhibitors, corticosteroids, and/or nonsteroidal immunosuppressants) showed no impacts of the concomitant use of each standard-of-care treatment on the efficacy of efgartigimod alfa [Table 53]. In Study 1704, 19 anti-AChR antibody-positive patients received concomitant cholinesterase inhibitors without corticosteroids or nonsteroidal immunosuppressants. The percentages of MG-ADL responders in these 19 patients were 16.7% (1 of 6 patients) in the placebo group and 84.6% (11 of 13 patients) in the efgartigimod alfa group, indicating that efgartigimod alfa is effective in patients who were receiving no concomitant immunosuppressants (corticosteroids or nonsteroidal immunosuppressants) as well.
- In Japan, polyethylene glycol-treated human normal immunoglobulin is approved as an IVIg for "the treatment of generalized myasthenia gravis (only for patients who are inadequately responsive to steroids or nonsteroidal immunosuppressants)," based on its efficacy and safety demonstrated in patients with gMG symptoms that are uncontrollable with existing treatments and require hemocatharsis. Eculizumab has been demonstrated to have efficacy and safety in (a) patients who failed to respond to ≥1 year-long therapy with ≥2 immunosuppressants, and (b) those who failed to respond to ≥1 immunosuppressant(s) and were on IVIg or plasmapheresis regularly for the management of muscle weakness at least once every 3 months in the past 12 months, and required to continue IVIg or plasmapheresis for disease control. Accordingly, eculizumab was approved for "treatment of patients with generalized myasthenia gravis (only for symptoms uncontrollable with high-dose intravenous immunoglobulin therapy or plasmapheresis)."
- Study 1704 on efgartigimod alfa did not include patients with no prior treatment for gMG. However, there was no clear inclusion criterion requiring patients to have been on particular gMG treatments or inadequately responsive to the treatment. The study results showed that the efficacy of efgartigimod alfa, based on the percentages of MG-ADL responders and QMG responders, was not affected by the concomitant use of respective standard-of-care treatment (cholinesterase inhibitors, corticosteroids, and/or nonsteroidal immunosuppressants). These findings suggest that a particular prior treatment-related condition will be unnecessary for the indication of efgartigimod alfa.
- Based on the above, efgartigimod alfa is intended for patients presenting with gMG symptoms from its early stage, and the target population does not need to be restricted to patients who are inadequately responsive to prior treatments with immunosuppressants (corticosteroids or nonsteroidal immunosuppressants). Accordingly, the indication of efgartigimod should be "the treatment of generalized myasthenia gravis."

PMDA's view:

- The results of Study 1704 involving patients with gMG demonstrated the efficacy and safety of efgartigimod alfa administered in addition to stable doses of their standard-of-care treatments (cholinesterase inhibitors, corticosteroids, and/or nonsteroidal immunosuppressants).
- Treatment of gMG is recommended to begin with low-dose oral corticosteroids or nonsteroidal immunosuppressants (*Japanese Clinical Guidelines for Myasthenia Gravis 2014*. Nankodo Co., Ltd., 2014).
- Based on the target populations of efgartigimod alfa in the clinical studies and on the Japanese Clinical Guidelines for Myasthenia Gravis, efgartigimod alfa should be administered to patients who have been treated with corticosteroids or nonsteroidal immunosuppressants.
- The appropriateness of the above indication of efgartigimod alfa in view of the target population will be concluded taking into account comments from the Expert Discussion.

7.R.6 Dosage and administration

PMDA asked the applicant to explain the appropriateness of the proposed dosage and administration, and efgartigimod alfa's response durability based on the results of the global phase III study (CTD 5.3.5.1-2, Study 1704) and the global long-term extension study (CTD 5.3.5.2-2, Study 1705).

The applicant's explanation:

- The dosage regimen of efgartigimod alfa used in Study 1704 was determined as 4 intravenous doses of 10 mg/kg once weekly based on the safety, pharmacokinetic, and pharmacodynamic (the decrease in IgG concentration) results from the foreign phase I study in healthy subjects (CTD 5.3.3.1-1, Study 1501) and the foreign phase II study in patients with gMG (CTD 5.3.5.1-1, Study 1602) [see Section 6.R.2].
- In Study 1602, 9[54)] of 12 patients receiving 4 intravenous doses of efgartigimod alfa 10 mg/kg once-weekly achieved a clinically significant improvement, as shown by a ≥2-point decrease in MG-ADL total score lasting for ≥6 weeks. This suggested that the clinical effect of efgartigimod alfa may be long lasting. In Study 1704, based on this finding, efgartigimod alfa was to be administered in intermittent treatment cycles, in which a new treatment cycle was initiated based on the clinical effect measured by the MG-ADL total score[40)] in individual patients. Given that the results of Study 1501 showed that the elimination half-life of efgartigimod alfa was 3 to 5 days, and the serum efgartigimod alfa concentration declined to below the quantitation limit by 5 weeks after the last dose, Study 1704 had a 5-week follow-up period after the last dose of efgartigimod alfa, during which the subsequent treatment cycle would not be initiated.
- Study 1704 successfully demonstrated a statistically significant difference in the primary endpoint, the percentage of MG-ADL responders during the first treatment cycle in the anti-AChR antibody-positive subpopulation, between the efgartigimod alfa group and the placebo group, and also showed a similar tendency in the overall population including both anti-AChR antibody-positive and -negative patients (Table 33). Table 59 presents the changes over time from baseline in MG-ADL total score during the first treatment cycle of Study 1704. The change from baseline in MG-ADL total score in the efgartigimod alfa group began to increase at Week 1 (1 week after the first dose of the study drug) as compared with the

54) Among the 9 patients in the efgartigimod alfa group, a ≥2-point decrease in MG-ADL total score was maintained for 6 weeks in 2 patients, and for 7 weeks in 1 patient. In the remaining 6 patients, a ≥2-point decrease was still observed at the end of the study, which precluded a determination of its exact duration. As of the end of the study, the decrease had been maintained for ≥7 weeks in 1 patient, ≥9 weeks in 1 patient, and ≥10 weeks in 4 patients.

placebo group and peaked at Week 4 (1 week after the last dose of the study drug). The percentage (mean ± SE) of the duration of a ≥2-point decrease in MG-ADL total score in the study period (126 days) was higher in the efgartigimod alfa group (58.2 ± 5.47%) than in the placebo group (39.6 ± 5.44%).

Table 59. Changes from baseline in MG-ADL total score during the first treatment cycle (Study 1704,[a)] mITT, overall population[b)])

		Placebo	Efgartigimod alfa
Baseline[a)]		8.8 ± 0.25 (83)	9.2 ± 0.29 (84)
Change from baseline	Week 1	-1.0 ± 0.20 (79)	-1.9 ± 0.29 (84)
	Week 2	-1.6 ± 0.22 (81)	-3.4 ± 0.33 (83)
	Week 3	-1.7 ± 0.27 (80)	-3.8 ± 0.34 (82)
	Week 4	-2.0 ± 0.27 (79)	-4.5 ± 0.36 (80)
	Week 5	-2.2 ± 0.28 (77)	-4.3 ± 0.35 (79)
	Week 6	-1.6 ± 0.32 (79)	-4.1 ± 0.32 (81)
	Week 7	-1.9 ± 0.28 (79)	-3.5 ± 0.33 (80)
	Week 8	-1.8 ± 0.31 (78)	-2.5 ± 0.35 (81)
	Week 10	-1.1 ± 0.35 (74)	-1.9 ± 0.43 (72)
	Week 12	-3.2 ± 0.56 (25)	-3.3 ± 0.54 (38)
	Week 14	-4.0 ± 0.58 (22)	-3.8 ± 0.56 (24)
	Week 16	-4.4 ± 0.50 (21)	-4.2 ± 0.52 (22)

Mean ± SE (n)

a) In Study 1704, a new treatment cycle was initiated after ≥8 weeks from the first dose of the study drug in the previous treatment cycle.

b) The overall population included both anti-AChR antibody-positive and -negative patients.

- In Study 1705, the therapeutic effect of efgartigimod alfa for patients with gMG lasted during repeated treatment cycles [Tables 35 and 36]. Although Study 1705 was designed to assess the necessity of retreatment every 4 weeks, according to the prespecified visit interval after the last dose of efgartigimod alfa, based on the MG-ADL total score,[44)] the necessity of retreatment was able to be determined at a shorter interval for patients with worsening symptoms. Actually, 5 of 139 patients in Study 1705 initiated ≥1 subsequent treatment cycles within <4 weeks after the last dose of efgartigimod alfa in the previous treatment cycle, which posed no clinically relevant safety concerns.
- In Study 1704, the median time (range) from the first dose of efgartigimod alfa in the first treatment cycle to the start of the second treatment cycle was 10 weeks (8 to 26 weeks). In Study 1705, the median time (range of the medians in 8 cycles) from the first dose of efgartigimod alfa to the start of the subsequent treatment cycle was approximately 7 to 9 weeks. The time course of the improvement in MG-ADL total score during each treatment cycle was consistent with that of the decrease in total IgG concentration, except in some patients who experienced a constant decrease in MG-ADL total score even after the recovery of total IgG concentration, indicating long-lasting effect of efgartigimod alfa.
- The clinical studies excluded patients with a total IgG concentration of <6 g/L to avoid the potential risks associated with excessively decreased IgG concentrations. However, the magnitude of the decrease in total IgG concentration by treatment with efgartigimod alfa and its restoration were almost constant, even when the number of treatment cycles increased. In addition, repeated treatment cycles caused no clinically relevant safety concerns such as serious infections [see Section 7.R.3.2]. Increased risk of severe and recurrent infections has been reported from patients with prolonged total IgG concentration of <1 g/L (*Semin Arthritis Rheum.* 2009;39:18-29). The trough total IgG concentrations observed in patients receiving efgartigimod alfa in the clinical studies remained mostly in the range from 2.5 to 3.5 g/L, and no patients had the total IgG concentration decreasing to <1 g/L.

- Based on the above, efgartigimod alfa should be administered at 10 mg/kg intravenously once weekly for 4 times, and the treatment should be continued in cycles depending on each patient's condition.

PMDA's view:

- Studies 1704 and 1705 demonstrated the efficacy and safety of efgartigimod alfa administered in repeated cycles based on individuals' MG-ADL total scores. Also, given the recovery of IgG concentration over time and the attenuated improvement in MG-ADL total score over time after the completion of treatment, retreatment with efgartigimod alfa is necessary and clinically meaningful. Thus, there are no particular problems with the applicant's explanation that efgartigimod alfa should be administered at 10 mg/kg intravenously once weekly for 4 times, and the treatment should be continued in cycles depending on the conditions of individuals.
- Taking into account that efgartigimod alfa decreases IgG concentration and possibly increases a risk of infections [see Section 7.R.3.2], the necessity of retreatment in another cycle should be determined after close observation of the magnitude of decrease in IgG concentration and the development of infections, etc. as well as clinical symptoms of gMG. The applicant should appropriately communicate the magnitude of decrease in IgG concentration, the occurrence of infections, the number of cycles repeated, etc. in the clinical studies to healthcare professionals.
- The above PMDA's conclusion will be finalized taking into account comments from the Expert Discussion.

7.R.7 Post-marketing investigations

The applicant's explanation:

To evaluate the safety of efgartigimod alfa in clinical practice, the applicant plans to conduct post-marketing surveillance, in the form of a specified use-results survey covering all patients treated with efgartigimod alfa. The target sample size for the survey will be ≤500 patients, and the observation period will be 12 months or until the completion of 6 treatment cycles, whichever comes first.

PMDA's view:

In view of the limited experiences in the use of efgartigimod alfa in Japanese patients in the global phase III study (CTD 5.3.5.1-2, Study 1704) and the global long-term extension study (CTD 5.3.5.2-2, Study 1705), etc., information about infections (including association with decreased immunoglobulin concentrations), infusion-related reactions, etc. should be further collected through post-marketing surveillance covering all patients treated with efgartigimod alfa. The appropriateness of the proposed post-marketing investigations will be finalized taking into account comments from the Expert Discussion.

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

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

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of

Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

The new drug application data (CTD 5.3.5.1-2, CTD 5.3.5.2-2) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

On the basis of the data submitted, PMDA has concluded that efgartigimod alfa has efficacy in the treatment of gMG, and that efgartigimod alfa has acceptable safety in view of its benefits. Efgartigimod alfa is clinically meaningful because it offers a new treatment option for patients with gMG. At the same time, PMDA considers that continued discussion is necessary on the efficacy in Japanese patients, and efficacy, safety, indication, dosage and administration, the appropriateness of post-marketing investigations, etc. in anti-AChR antibody-negative patients.

PMDA has concluded that efgartigimod alfa may be approved if efgartigimod alfa is considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

November 16, 2021

Product Submitted for Approval

Brand Name	Vyvgart for Intravenous Infusion 400 mg
Non-proprietary Name	Efgartigimod Alfa (Genetical Recombination)
Applicant	Argenx Japan K.K.
Date of Application	April 19, 2021

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 the Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Evaluation based on the results of the global clinical studies

PMDA's view about differences in the efficacy and safety of efgartigimod alfa between Japanese and non-Japanese patients in the global phase III study in patients with generalized myasthenia gravis (gMG) (CTD 5.3.5.1-2, Study 1704) [see Section 7.R.1.2 of the Review Report (1)].

Efficacy:

According to the following outcomes, there are no major problems with evaluating the efficacy of efgartigimod alfa in Japanese patients with gMG based on the results from the overall population of Study 1704.

- The results of Study 1704 revealed inconsistency in the primary endpoint results between the Japanese and non-Japanese subpopulations. In the global long-term extension study (CTD 5.3.5.2-2, Study 1705), the change in MG-ADL total score from baseline to the last dose of efgartigimod alfa in each treatment cycle tended to be small in the Japanese subpopulation as compared with the non-Japanese subpopulation.
- However, the assessment of over-time change in MG-ADL total score in individual Japanese patients showed that the percentage of patients achieving a ≥2-point decrease in MG-ADL total score, which is considered a clinically significant improvement, was higher in the efgartigimod alfa group than in the placebo group, and that the duration of the ≥2-point decrease in MG-ADL total score in the study period (126 days) tended to be long in the efgartigimod alfa group as compared with the placebo group.
- In Study 1705, the change in QMG total score in the Japanese subpopulation was comparable to that in the non-Japanese subpopulation. In Study 1704, the changes in the concentrations of total IgG and the IgG

subclasses in the Japanese subpopulation showed tendencies similar to those in the non-Japanese subpopulation.

Safety:
Despite the limited number of patients, the safety data from Japanese patients
in Study 1704 revealed no safety concerns specific to Japanese patients.

Based on these results, the efficacy and safety of efgartigimod alfa in Japanese patients can be evaluated based on the results from the overall populations of Studies 1704 and 1705, the global studies of efgartigimod alfa.

The expert advisors generally supported the above PMDA's conclusion, while making the following remarks [for post-marketing information collection, see Section "1.6 Risk management plan (draft)"].

- Probably due to the rarity of gMG and the limited number of Japanese patients enrolled in Study 1704, some data from the Japanese subpopulation failed to evidently demonstrate the efficacy of efgartigimod alfa. However, a comprehensive interpretation of the efficacy results, including the results of secondary endpoints such as QMG total score and total IgG concentration, showed the promising efficacy of efgartigimod alfa in the Japanese subpopulation. Thus, there are no problems with evaluating the efficacy of efgartigimod alfa in Japanese patients based on the results from the overall population of the study.
- Given the limited experiences in the use in Japanese patients and novel action mechanism of efgartigimod alfa, information from post-marketing surveillance is important.

1.2 Efficacy

PMDA's view about the efficacy of efgartigimod alfa in anti-AChR antibody-positive and -negative patients, based on the results of the global phase III study (CTD 5.3.5.1-2, Study 1704) and the global long-term extension study (CTD 5.3.5.2-2, Study 1705) [see Section 7.R.2.1 of the Review Report (1)]:

- Patients with anti-AChR antibody-positive gMG: The percentage of MG-ADL responders during the first treatment cycle in the anti-AChR antibody-positive subpopulation, the primary endpoint for Study 1704, was statistically significantly high in the efgartigimod alfa group as compared with the placebo group. Thus, the efficacy of efgartigimod alfa has been demonstrated in anti-AChR antibody-positive patients.
- Patients with anti-AChR antibody-negative gMG: The percentage of MG-ADL responders during the first treatment cycle in the anti-AChR antibody-negative subpopulation of Study 1704 was high in the placebo group, and no substantial difference was observed between efgartigimod alfa and the placebo. The limited number of anti-AChR antibody-negative patients in Study 1704 hindered the identification of causative factors in the higher percentage of MG-ADL responders in the placebo group than in the efgartigimod alfa group of this subpopulation. However, the applicant explained that the percentage of responders on the QMG total score, which is a physician-rated outcome measure based on quantitative test results, in the anti-AChR antibody-negative subpopulation tended to be high in the efgartigimod alfa group as compared with the placebo group. This suggests that the MG-ADL total score, a patient-reported outcome measure, was likely to have produced a high placebo response, and that this might have been a contributing factor. This applicant's explanation is understandable. In the anti-AChR antibody-negative

subpopulation of Study 1704, the percentage of QMG responders tended to be high in the efgartigimod alfa group as compared with the placebo group. In Study 1704 and its extension study, Study 1705, the changes in MG-ADL total score and QMG total score decreased following the administration of efgartigimod alfa in both the anti-AChR antibody-positive and -negative subpopulations, with no substantial differences between the subpopulations.

- The anti-AChR antibody-negative subpopulation included anti-MuSK antibody-positive patients as well as anti-MuSK antibody-negative and anti-LRP4 antibody-positive (double-seronegative) patients. In view of IgG autoantibody expression suggested as the cause of the pathological condition of gMG in these patients, concentrations of IgG subclasses including pathogenic IgG autoantibodies decreased by efgartigimod alfa, and proven benefits of plasmapheresis in anti-AChR antibody-negative patients, the applicant's explanation about promising efficacy of efgartigimod alfa in anti-AChR antibody-negative patients, including anti-MuSK antibody-positive patients, is understandable.
- Despite the limited number of anti-AChR antibody-negative patients, the safety assessment for efgartigimod alfa by anti-AChR antibody status in Studies 1704 and 1705 suggested no safety concerns specific to anti-AChR antibody-negative patients.
- Accordingly, the efficacy of efgartigimod alfa is promising in patients with anti-AChR antibody-negative gMG as well. Therefore, efgartigimod alfa can be intended not only for anti-AChR antibody-positive patients but also for anti-AChR antibody-negative patients.

The expert advisors generally supported the above PMDA's conclusion and made the following remark [for post-marketing information collection from anti-AChR antibody-negative patients, see Section "1.6 Risk management plan (draft)"].

- The inclusion of anti-AChR antibody-negative patients in the intended population for efgartigimod alfa will not be a problem. However, due to the extremely limited experiences in the use of efgartigimod alfa in anti-AChR antibody-negative patients in the clinical studies, the collection of post-marketing safety and efficacy data of efgartigimod alfa from this patient population is important.

1.3 Safety

PMDA's view:

Based on the submitted clinical study results, the safety risks associated with the use of efgartigimod alfa are considered acceptable. In the global phase III study (CTD 5.3.5.1-2, Study 1704), the incidence of infection-related adverse events was high in the efgartigimod alfa group as compared with the placebo group, with a tendency of high incidences of upper respiratory tract infection and urinary tract infection, etc. In patients receiving efgartigimod alfa in the foreign phase II study (CTD 5.3.5.1-1, Study 1602), Study 1704, and the global long-term extension study (CTD 5.3.5.2-2, Study 1705), the incidences of infection-related adverse events by quartiles of trough total IgG concentration tended to be high in patients with a trough total IgG concentration below the median (2.52 g/L) as compared with those with a trough total IgG concentration above the median. In the same population, the incidences of infection-related adverse events tended to be high in patients with a trough total IgG concentration of <3.0 g/L as compared with those with a concentration of ≥3.0 g/L. Patients with a trough total IgG concentration of <3.0 g/L also tended to have increased risk of serious

infections. Given these outcomes, PMDA has concluded that treatment with efgartigimod alfa is likely to cause or worsen infections through decreased IgG concentrations and also requires attention to MG crisis associated with infections. Therefore, the package insert should provide a cautionary note on the need for careful observation of patient condition, including appropriate IgG concentration monitoring.

The expert advisors generally supported the above PMDA conclusion, while making the following remark.

- Due to its action mechanism, the major safety concern is high susceptibility to infections due to decreased IgG concentration by efgartigimod alfa. In the clinical studies, high incidences of upper respiratory tract infection and urinary tract infection were observed, and the possibility cannot be denied that these infections may induce MG crisis. Therefore, the package insert should advise IgG concentration monitoring. In addition, due to the limited data from the clinical studies, information about the occurrence of infections including their severity should be collected in the post-marketing setting to investigate their association with IgG concentration.

Based on the above discussion, PMDA instructed the applicant to provide the following cautionary note in the "Important Precautions" section of the package insert, and the applicant responded appropriately [for post-marketing information collection for infections, see Section "1.6 Risk management plan (draft)"].

Important Precautions

Treatment with efgartigimod alfa lowers blood IgG concentration and may cause or worsen infections. Patient's clinical condition should be closely monitored through blood tests, etc. on a regular basis during and after the treatment. Patients should be advised to stay vigilant for the signs and symptoms of infections and immediately contact healthcare professionals in case of any abnormalities.

1.4 Clinical positioning and indication

PMDA's view about the clinical positioning of efgartigimod alfa [see Section 7.R.4 of the Review Report (1)]:
Efgartigimod alfa is an FcRn-targeted human IgG1 antibody Fc fragment with modified amino acid residues. With its action mechanism different from conventional gMG drugs, efgartigimod alfa inhibits FcRn-mediated IgG recycling and decreases the concentrations of IgG, including pathogenic IgG autoantibodies. In view of the submitted clinical study results, etc., efgartigimod alfa is clinically significant because it offers a new treatment option for patients with gMG.

PMDA's view about the indication of efgartigimod alfa [see Section 7.R.5 of the Review Report (1)]:

- The global phase III study (CTD 5.3.5.1-2, Study 1704) targeted patients with gMG who had generalized symptoms, with a MG-ADL total score of ≥5 points and >50% of the total score attributable to non-ocular symptoms. The results demonstrated the efficacy and safety of efgartigimod alfa administered in addition to stable doses of their standard-of-care treatments (cholinesterase inhibitors, corticosteroids, and/or nonsteroidal immunosuppressants). The study therefore did not include patients who had not been treated for gMG.

- The Japanese Clinical Guidelines for Myasthenia Gravis recommend that gMG therapy should begin with low-dose oral corticosteroids or nonsteroidal immunosuppressants (*Japanese Clinical Guidelines for Myasthenia Gravis 2014*. Nankodo Co., Ltd., 2014).
- The inclusion criteria of Study 1704 did not clearly require participants to have received particular gMG treatments or be inadequately responsive to the treatments. However, given the patient population of Study 1704 and the recommendation by the Japanese Clinical Guidelines for Myasthenia Gravis, efgartigimod alfa should be administered to patients who are receiving corticosteroids or nonsteroidal immunosuppressants and inadequately responsive to the treatments.

At the Expert Discussion, the expert advisors generally supported the above PMDA's conclusions, while expressing the following their views.

- Although the existing drugs have been shown to contribute to better control of gMG symptoms, these treatments are not options for patients with refractory gMG due to adverse drug reactions, etc. With its novel action mechanism, efgartigimod alfa is expected to improve the patients' QOL, and the introduction of efgartigimod alfa into clinical settings is thus considered highly clinically meaningful.
- The indication of efgartigimod alfa is appropriate as it has been defined same as that of intravenous immunoglobulin (IVIg), in light of their similar positions.
- The use of efgartigimod alfa, as compared with IVIg, has not been shown to pose a significant risk of infections, etc. in the clinical studies. Nevertheless, potential infection risk of efgartigimod alfa remains unknown for its novel action mechanism, when used in a broad range of patients in the post-marketing setting. Currently, the efficacy and safety data of efgartigimod alfa particularly from Japanese patients are extremely limited. In contrast, IVIg has been used for a long time and shown to be effective in a broader range of patients, with no particularly great safety concerns except for rare anaphylaxis cases. Given this situation, it is unlikely that efgartigimod alfa will preferentially be used over IVIg for the time being after approval, and familiar IVIg will remain the preferred choice. However, IVIg needs to be intravenously infused for 5 consecutive days starting on Day 1 at a low rate and be gradually increased while monitored for adverse drug reactions or any other abnormalities. In contrast, efgartigimod alfa is infused over 1 hour once weekly for 4 times. With this advantage, i.e., shorter infusion time of each dose than IVIg, efgartigimod alfa may become the preferred choice over IVIg when more post-marketing safety and efficacy data are available.
- For patients with newly-diagnosed severe gMG, particularly when accompanied by MG crisis, steroid pulse therapy, hemocatharsis or IVIg, and immunosuppressants are often administered almost simultaneously. The safety or efficacy of efgartigimod alfa administered to patients with MG crisis has not been evaluated in any clinical study, and there are no data from clinical studies directly comparing efgartigimod alfa and IVIg or hemocatharsis. Efgartigimod alfa may take longer time to exert its effect than IVIg and therefore is not recommended over IVIg for the treatment of MG crisis. However, in the future, efgartigimod alfa can be an additional option for patients with MG crisis backed by accumulated post-marketing experiences.

Accordingly, PMDA instructed the applicant to modify the description of "Indication" as presented below, and the applicant responded appropriately.

Indication

Generalized myasthenia gravis (only for patients who are not adequately responsive to steroids or nonsteroidal immunosuppressants)

1.5 Dosage and administration

PMDA's view:

- There were no problems with the dosage regimen of efgartigimod alfa in the global phase III study (CTD 5.3.5.1-2, Study 1704), i.e., 4 once-weekly intravenous doses of 10 mg/kg, based on the safety, pharmacokinetic, and pharmacodynamic (the decrease in IgG concentration) results from a foreign phase I study in healthy subjects (CTD 5.3.3.1-1, Study 1501) and a foreign phase II study in patients with gMG (CTD 5.3.5.1-1, Study 1602) [see Section 6.R.2 of the Review Report (1)].
- The MG-ADL total score-based efficacy in individual patients and the safety of efgartigimod alfa in repeated cycle treatment have been demonstrated by the results of Studies 1704 and its long-term extension study (CTD 5.3.5.2-2, Study 1705). Also, given the gradual recovery of decreased IgG concentration and gradually attenuated improvement in MG-ADL total score after the completion of treatment with efgartigimod alfa, retreatment with efgartigimod alfa is necessary and clinically meaningful. Accordingly, there are no particular problems with the applicant's explanation that efgartigimod alfa should be administered at an intravenous dose of 10 mg/kg once weekly for 4 times in cycles, depending on the individuals' condition [see Section 7.R.6 of the Review Report (1)].
- Efgartigimod alfa decreases IgG concentrations and is expected to increase the risk of infections. The need for retreatment in subsequent cycles should be determined after careful observation of the patient's condition, such as the magnitude of the decrease in IgG concentration, the onset of infections, and clinical gMG symptoms. Therefore, the applicant should appropriately communicate the magnitude of the decrease in IgG concentration, the occurrence of infections, etc. observed in the clinical studies to healthcare professionals [see Section 7.R.6 of the Review Report (1)].
- In Study 1705, with regard to the time to subsequent treatment cycles, whether retreatment was necessary was determined every 4 weeks (prespecified visit interval after the last dose of efgartigimod alfa) based on the MG-ADL total score in the previous treatment cycle. However, for patients with worsened symptoms, the decision on the retreatment could be made in a shorter term. In fact, 5 of 139 patients in Study 1705 initiated ≥1 new treatment cycles within <4 weeks after the last dose in the previous treatment cycle, which caused no clinically relevant safety concerns. Therefore, the applicant should advise that subsequent treatment cycles should be initiated according to the clinical gMG symptoms, etc. of each patient [see Section 7.R.6 of the Review Report (1)].

At the Expert Discussion, the expert advisors generally supported the above PMDA's conclusions, while making the following remark.

- The clinical studies were designed without a specific minimum dosing interval of efgartigimod alfa between the last dose in the previous cycle and the first dose in the subsequent cycle (cycle interval), and whether to retreat was determined based on the MG-ADL total score. Given this, a specific cycle interval will need not

be necessary. However, due to the extremely limited efficacy and safety data, the magnitude of increased risk of infections remains unknown during treatment with shorter cycle intervals, in which a new cycle begins before the IgG concentration returns to baseline, consequently prolonging the state of low IgG concentration. Therefore, offering information about cycle intervals in the clinical studies is meaningful.

Based on the above discussion, PMDA instructed the applicant to modify the proposed "Dosage and Administration" and "Precautions for Dosage and Administration" sections of the package insert as presented below, and to provide information about the cycle intervals in Studies 1704 and 1705 in the "Clinical Studies" section. The applicant responded appropriately.

Dosage and Administration

The usual adult dosage is 10 mg/kg of efgartigimod alfa (genetical recombination) administered as an intravenous infusion over 1 hour for 4 times at weekly intervals. This treatment cycle is repeated.

Precautions for Dosage and Administration

The need for subsequent treatment cycles should be determined based on clinical symptoms, etc.

1.6 Risk management plan (draft)

In view of the discussions presented in Section "7.R.7 Post-marketing investigations" of the Review Report (1) and comments from the expert advisers at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for efgartigimod alfa should include the safety specifications presented in Table 60, and that the applicant should conduct the additional pharmacovigilance activities and additional risk minimization activities presented in Table 61.

Table 60. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
・Infections ・Infusion reactions	None	None
Efficacy specification		
None		

Table 61. Summary of additional pharmacovigilance activities and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
・Early post-marketing phase vigilance ・Use-results survey (all-case surveillance)	・Disseminate data gathered during early post-marketing phase vigilance ・Prepare and disseminate an information leaflet for healthcare professionals (proper use guidelines) ・Prepare and disseminate an information leaflet for patients

Based on the following comment from the Expert Discussion, PMDA requested the applicant to conduct post-marketing surveillance to investigate the issues shown above.

- In view of the extremely limited use of efgartigimod alfa in anti-AChR antibody-negative patients in the clinical studies, etc., patient enrollment should be continued until a certain number of anti-AChR antibody-negative patients are secured to collect safety and efficacy data of patients including anti-AChR antibody-negative patients. Efgartigimod alfa has a novel mechanism of action. Therefore, surveillance results, including the incidence of infections, should be promptly communicated to healthcare professional, in the form of an interim analysis data at an appropriate data cutoff date.

The applicant's explanation:

Table 62 outlines the specified use-results survey to be implemented in patients with gMG. An interim analysis will be performed with the data cutoff date when data from 200 patients are available, and the analysis results will be promptly communicated to healthcare professionals.

Table 62. Outline of the specified use-results survey (draft)

Objective	To collect information about the safety and efficacy of efgartigimod alfa in clinical use
Survey method	All-case surveillance
Population	Patients with gMG treated with efgartigimod alfa
Observation period	≤3 years
Planned sample size	500 patients (including 100 anti-AChR antibody-negative patients)
Main survey items	Patient characteristics (age, gender, body weight, time of diagnosis, complications, antibody tests [anti-AChR antibodies, anti-MuSK antibodies], MGFA Classification, prior history of MG crisis/recurrent gMG symptoms, etc.) Prior treatments and concomitant treatments Vaccination status Exposure to efgartigimod alfa (administration days, dose, reasons for treatment discontinuation, etc.) Clinical deterioration (MG crisis, need for rescue therapy, recurrence of gMG symptoms) Efficacy (MG-ADL total score, QMG total score) Laboratory data (IgG concentration, etc.) Adverse events

PMDA accepted the above survey plan but considers that the results of the survey should be promptly communicated to healthcare professionals.

1.7 Current status of the ongoing clinical study

PMDA asked the applicant to explain the updated incidence of adverse events.

The applicant's explanation:

The incidences of infection-related adverse events by quartiles of trough total IgG concentration during treatment cycles in patients receiving efgartigimod alfa in the foreign phase II study (CTD 5.3.5.1-1, Study 1602), the global phase III study (CTD 5.3.5.1-2, Study 1704), and the global long-term extension study (CTD 5.3.5.2-2, Study 1705) [Table 57[55] of the Review Report (1)] were updated based on the latest data (data cutoff in February 2021) and are presented in Table 63. PMDA has confirmed that the updated incidences do not differ substantially from the incidences presented in Table 57.

Table 63. Incidences of infection-related infections by quartiles of trough total IgG concentration (patients receiving efgartigimod alfa in Studies 1602, 1704, and 1705)

	≤25 percentile[a]	>25 percentile to ≤50 percentile[b]	>50 percentile to ≤75 percentile[c]	>75 percentile
N	43	39	40	40
All adverse events	24 (55.8)	25 (64.1)	23 (57.5)	18 (45.0)
Serious adverse events	1 (2.3)	2 (5.1)	3 (7.5)	0
Adverse events leading to drug discontinuation	0	1 (2.6)	1 (2.5)	0
Common adverse events				
Nasopharyngitis	6 (14.0)	5 (12.8)	5 (12.5)	8 (20.0)
Upper respiratory tract infection	5 (11.6)	2 (5.1)	5 (12.5)	0
Urinary tract infection	3 (7.0)	5 (12.8)	4 (10.0)	4 (10.0)
Cystitis	2 (4.7)	1 (2.6)	0	0
Bronchitis	2 (4.7)	4 (10.3)	0	2 (5.0)
Herpes zoster	2 (4.7)	1 (2.6)	1 (2.5)	2 (5.0)
Pharyngitis	2 (4.7)	1 (2.6)	1 (2.5)	0
Pneumonia	2 (4.7)	0	0	1 (2.5)
Hordeolum	2 (4.7)	0	0	0
Oral herpes	1 (2.3)	1 (2.6)	2 (5.0)	0
Influenza	1 (2.3)	3 (7.7)	0	1 (2.5)
Respiratory tract infection	1 (2.3)	1 (2.6)	2 (5.0)	0
Gastroenteritis	0	1 (2.6)	0	2 (5.0)
Gingivitis	0	2 (5.1)	1 (2.5)	0
COVID-19	0	3 (7.7)	1 (2.5)	2 (5.0)
Gastroenteritis viral	0	0	2 (5.0)	0
Pharyngitis streptococcal	0	2 (5.1)	0	0
Conjunctivitis	0	2 (5.1)	0	0
Tracheitis	0	0	2 (5.0)	0

n (incidence [%]), the quartiles of trough total IgG concentration and the incidences of infection-related adverse events are based on the results as of the data cutoff in February 2021.
a) Total IgG concentration (25th percentile), 1.99 g/L; b) Total IgG concentration (50th percentile), 2.49 g/L;
c) Total IgG concentration (75th percentile), 3.24 g/L

In Study 1705, no patients died from adverse events between the data cutoff in February 2021 and [redacted], 202[redacted]. The serious adverse events other than deaths reported during this period are presented in Table 64. As compared with the occurrence of serious adverse events that have been reported in clinical trials [see Section 7.R.1.2 of the Review Report (1)], no new safety concerns have been suggested.

55) The quartiles of trough total IgG concentration are based on the results at the data cutoff in April 2020, while the incidences of infection-related adverse events are based on the results at the data cutoff in October 2020.

PMDA's view:

PMDA has concluded that no new safety concerns regarding long-term treatment with efgartigimod alfa have been identified since the data cutoff.

Table 64. Serious adverse events other than deaths

Events
COVID-19 and myasthenia gravis in 2 patients each, and COVID-19/acute respiratory failure, shoulder arthroplasty, procedural headache*/infusion related reaction*/nausea,* retinal detachment, atrial fibrillation, cerebral venous sinus thrombosis, and pseudomonal sepsis in 1 patient each

*Events for which a causal relationship to the study drug could not be ruled out

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the proposed indication and dosage and administration modified as follows, with the approval conditions below.

The product is an orphan drug, and the re-examination period is thus 10 years. The product is classified as a biological product, and both the drug product and its drug substance are classified as powerful drugs.

Indication Generalized myasthenia gravis (only for patients who are not adequately responsive to steroids or nonsteroidal immunosuppressants)

Dosage and Administration The usual adult dosage is 10 mg/kg of efgartigimod alfa (genetical recombination) administered as an intravenous infusion over 1 hour for 4 times at weekly intervals. This treatment cycle is repeated.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because of the limited data from Japanese clinical studies, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, until data are collected from a specified number of patients, to understand the characteristics of patients treated with the product and obtain safety and efficacy data early so as to take necessary measures for the product to be used properly.

Appendix

List of Abbreviations

ABDEG	Antibody that enhances Degradation
AChR	Acetylcholine Receptor
ADA	Anti-Drug Antibody
A/G	Albumin/Globulins
ALT	Alanine aminotransferase
AUC	Area under the concentration-time curve
CD107	Cluster of Differentiation 70
CE-SDS	Capillary gel Electrophoresis with Sodium Dodecyl Sulfate
CHO	Chinese Hamster Ovary
CL	Clearance
C_{max}	maximum observed Concentration
COVID-19	Coronavirus Disease 2019
CQA	Critical Quality Attribute
C_{trough}	serum Concentration observed prior to start of infusion
C1q	Complement protein 1q
DNA	Deoxyribonucleic Acid
EC_{50}	Half Maximal Effective Concentration
Efgartigimod alfa/ efgartigimod alfa	Patients who were assigned to the efgartigimod alfa group in Study 1704 and received efgartigimod alfa in Study 1705
EFTE	Ethylene-tetrafluoroethylene co-polymer
eGFR	estimated Glomerular Filtration Rate
ELISA	Enzyme-linked Immunosorbent Assay
EOPC	End of Production Cells Bank
FcRn	Neonatal Fc Receptor
FcγR	Fc gamma Receptor
FOB	Functional Observational Battery
gMG	generalized Myasthenia Gravis
GP-HPLC	Gel Permeation-High Performance Liquid Chromatography
HCP	Host Cell Protein
[redacted] HPLC	[redacted] High Performance Liquid Chromatography
[redacted]	[redacted]
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICH Q5A (R1) Guidelines	Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin (PMSB/ELD Notification No. 329 dated February 22, 2000)
ICH Q5B Guidelines	Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products (PMSB/ELD Notification No. 3 dated January 6, 1998)
ICH Q5D Guidelines	Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products (PMSB/ELD Notification No. 873 dated July 14, 2000)
icIEF	Capillary Isoelectric Focusing
Ig	Immunoglobulin
ITT	Intention to Treat
IVIg	Intravenous Immunoglobulin
K_d	Equilibrium Dissociation Constant
[redacted]	[redacted]
LRP4	Low-density lipoprotein receptor-related Protein 4
LUC	Large Unstained Cell(s)

MCB	Master Cell Bank
MedDRA	Medical Dictionary for Regulatory Activities
MG	Myasthenia Gravis
MG-ADL	Myasthenia Gravis Activities of Daily Living
MGFA	Myasthenia Gravis Foundation of America
mITT	modified intent-to-treat
MuSK	Muscle-specific receptor tyrosine Kinase
NK	Natural Killer
NZW	New Zealand White
PBS	Phosphate-buffered Saline
PCR	Polymerase Chain Reaction
pH	potential Hydrogen
Placebo/ efgartigimod alfa	Patients who were assigned to the placebo group in Study 1704 and received efgartigimod alfa in Study 1705
PMDA	Pharmaceuticals and Medical Devices Agency
QbD	Quality by Design
QMG	Quantitative Myasthenia Gravis
QOL	Quality of Life
RH	Relative Humidity
SOC	System Organ Class
SPR	Surface Plasmon Resonance
Study 1501	Study ARGX-113-1501 (CTD 5.3.3.1-1)
Study 1602	Study ARGX-113-1602 (CTD 5.3.5.1-1)
Study 1702	Study ARGX-113-1702 (Reference CTD 5.3.3.1-2)
Study 1704	Study ARGX-113-1704 (CTD 5.3.5.1-2)
Study 1705	Study ARGX-113-1705 (CTD 5.3.5.2-2)
$t_{1/2}$	Elimination Half-life
t_{max}	Time to maximum Concentration
Vss	Volume of distribution at steady-state
Vz	Volume of distribution at terminal phase
WCB	Working Cell Bank