Report on the Deliberation Results

August 25, 2023

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau

Ministry of Health, Labour and Welfare

Brand Name	Zilbrysq Syringe for S.C. Injection 16.6 mg Zilbrysq Syringe for S.C. Injection 23.0 mg Zilbrysq Syringe for S.C. Injection 32.4 mg
Non-proprietary Name	Zilucoplan Sodium (JAN*)
Applicant	UCB Japan Co., Ltd.
Date of Application	December 8, 2022

Results of Deliberation

In its meeting held on August 21, 2023, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

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

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because data from Japanese clinical studies are very limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product to keep track of information on patient characteristics until data from a specified number of patients have been accrued. Furthermore, data on the safety and efficacy of the product should be collected as soon as possible, and measures to ensure proper use of the product should also be taken.
3. The applicant is required to take necessary post-marketing measures to ensure that the product will be administered only under the supervision of a physician who is familiar with the diagnosis and treatment of generalized myasthenia gravis and is also fully capable of managing the risks etc. associated with the product at a medical institution that can respond to such risks, in close coordination with a physician who is well versed with the diagnosis and treatment of meningococcal infections.

**Japanese Accepted Name (modified INN)*

Review Report

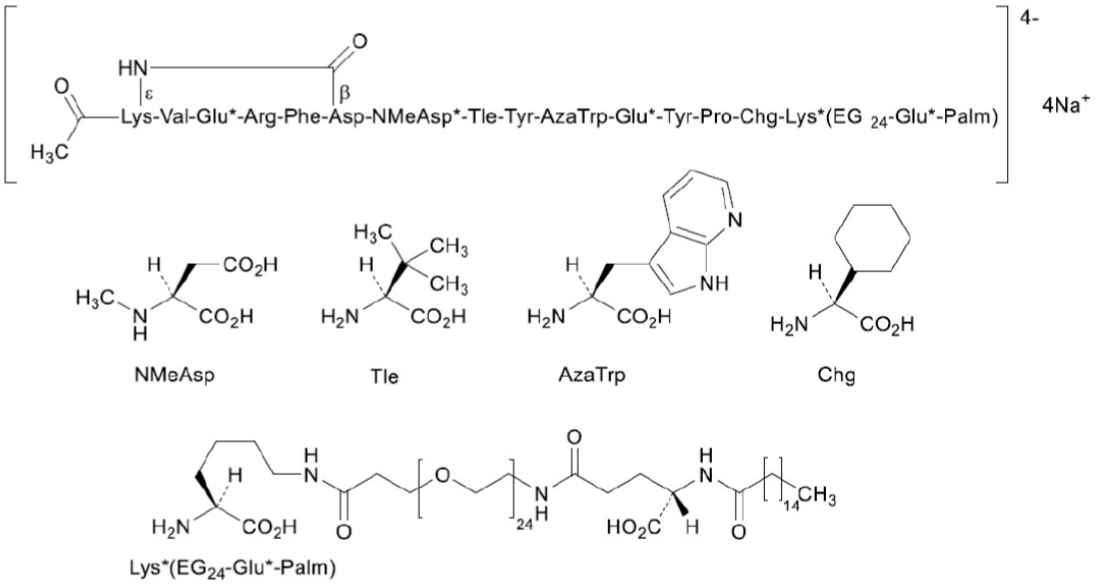
August 9, 2023

Pharmaceuticals and Medical Devices Agency

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

Brand Name	Zilbrysq Syringe for S.C. Injection 16.6 mg Zilbrysq Syringe for S.C. Injection 23.0 mg Zilbrysq Syringe for S.C. Injection 32.4 mg
Non-proprietary Name	Zilucoplan Sodium
Applicant	UCB Japan Co., Ltd.
Date of Application	December 8, 2022
Dosage Form/Strength	Solution for injection: Each syringe contains 17.0 mg of zilucoplan sodium (equivalent to zilucoplan 16.6 mg), 23.6 mg of zilucoplan sodium (equivalent to zilucoplan 23.0 mg), or 33.2 mg of zilucoplan sodium (equivalent to zilucoplan 32.4 mg).
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



* Amino acids with acidic groups. The protonated arginine side chain is bound to one of the acidic groups and a sodium ion is bound to each of the 4 acidic groups.

Molecular formula: $C_{172}H_{274}N_{24}Na_4O_{55}$

Molecular weight: 3650.10

Chemical name: Tetrasodium salt of N^2-acetyl-L-lysyl-L-valyl-L-α-glutamyl-L-arginyl-L-phenylalanyl-L-α-aspartyl-*N*-methyl-L-α-aspartyl-3-methyl-L-valyl-L-tyrosyl-3-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-L-alanyl-L-α-glutamyl-L-tyrosyl-L-prolyl-(2*S*)-2-cyclohexylglycyl-N^6-(3-{ω-[(*N*-hexadecanoyl-L-γ-glutamyl)amino]tetracosakis(oxyethylene)-α-yl}propanoyl)-L-lysine (6→1^6)-lactam

Items Warranting Special Mention None

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 in patients who inadequately respond to corticosteroids 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 conditions.

Indication

Generalized myasthenia gravis (only in patients who inadequately respond to corticosteroids or nonsteroidal immunosuppressants)

Dosage and Administration

The usual adult dosage of zilucoplan administered as a subcutaneous injection once daily is determined based on the table below.

Body weight	Dosage
<56 kg	16.6 mg
≥56 kg and <77 kg	23.0 mg
≥77 kg	32.4 mg

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because data from Japanese clinical studies are very limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product to keep track of information on patient characteristics until data from a specified number of patients have been accrued. Furthermore, data on the safety and efficacy of the product should be collected as soon as possible, and measures to ensure proper use of the product should also be taken.
3. The applicant is required to take necessary post-marketing measures, to ensure that the product will

be administered only under the supervision of a physician who is familiar with the diagnosis and treatment of generalized myasthenia gravis and is also fully capable of managing the risks etc. associated with the product at a medical institution that can respond to such risks, in close coordination with a physician who is well versed with the diagnosis and treatment of meningococcal infections.

Attachment

Review Report (1)

July 12, 2023

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

Product Submitted for Approval

Brand Name	Zilbrysq Syringe for S.C. Injection 16.6 mg Zilbrysq Syringe for S.C. Injection 23.0 mg Zilbrysq Syringe for S.C. Injection 32.4 mg
Non-proprietary Name	Zilucoplan Sodium
Applicant	UCB Japan Co., Ltd.
Date of Application	December 8, 2022
Dosage Form/Strength	Solution for injection: Each syringe contains 17.0 mg of zilucoplan sodium (equivalent to zilucoplan 16.6 mg), 23.6 mg of zilucoplan sodium (equivalent to zilucoplan 23.0 mg), or 33.2 mg of zilucoplan sodium (equivalent to zilucoplan 32.4 mg).
Proposed Indication	Generalized myasthenia gravis
Proposed Dosage and Administration	The usual adult dosage is 0.3 mg/kg of zilucoplan administered as a subcutaneous injection once daily

Table of Contents

List of Abbreviations

See Appendix.

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

Zilbrysq is a solution for injection containing zilucoplan sodium (hereinafter referred to as "zilucoplan") as an active ingredient, and zilucoplan is a cyclic peptide containing 15 amino acids developed by Ra Pharmaceuticals, Inc.

Myasthenia gravis (MG) is an autoimmune disease characterized by weakness and rapid fatigue of skeletal muscles (e.g., ocular muscles, bulbar muscles, limb muscles, and respiratory muscles) that are caused by pathogenic autoantibody-mediated inhibition of the binding of the neurotransmitter acetylcholine to its receptors at the neuromuscular junction. In Japan, MG is a designated intractable disease. Myasthenia gravis is classified into 2 types: ocular MG, in which symptoms are localized to ocular muscles (e.g., eyelid ptosis and diplopia), and generalized MG (gMG), which involves generalized muscles. In Japan, patients with ocular MG and those with gMG account for approximately 20% and 80% of all MG patients, respectively (*Clin Exp Neuroimmunol.* 2014;5:84-91). Generalized MG affects the voluntary muscles throughout the body, and patients with gMG present with movement, speech, swallowing, and respiratory disorders, and other symptoms (*N Engl J Med.* 2016;375:2570-81, *Nat Rev Dis Primers.* 2019;5:30). Published literature has reported that approximately 15% to 20% of patients with MG develop respiratory failure requiring non-invasive positive pressure ventilation or mechanical ventilator support (i.e., myasthenic crisis) (*J Neurol Sci.* 2007;261:127-33).

Zilucoplan acts by binding to complement component 5 (C5) to inhibit the cleavage of C5 to C5a and C5b and binding of C5b and C6 and thereby preventing the formation of the membrane attack complex (MAC), which is considered involved in the pathogenesis of MG, at the neuromuscular junction, and reducing the disruption of neuromuscular transmission. In this way, zilucoplan is expected to be effective in the treatment of gMG.

The clinical development of zilucoplan for the treatment of gMG was initiated in [redacted] 20[redacted]. An application for marketing approval of zilucoplan has been filed by the applicant with data including the results from the global phase III study conducted in several regions including Japan.

Outside Japan, marketing applications for zilucoplan were filed in [redacted] 20[redacted] in the US and Europe. The applications are under review as of [redacted] 20[redacted]. Zilucoplan has yet to be approved in any country or region.

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white to slightly yellow powder. Its description, crystalline characteristics, solubility, partition coefficient, isoelectric point, hygroscopicity, optical rotation, and asymmetric center have been determined.

The chemical structure of the drug substance has been elucidated by ultraviolet spectroscopy (UV), fluorescence spectroscopy, proton nuclear magnetic resonance spectroscopy (^{1}H-NMR), carbon-13 (^{13}C-)

NMR, nitrogen-15 (^{15}N-) NMR, chiral amino acid analysis (gas chromatography-mass spectrometry [GC-MS]), amino acid analysis (high performance liquid chromatography [HPLC]), mass spectrometry (MS), X-ray powder diffraction, optical rotation, solubility, thermogravimetric analysis, water vapor sorption, circular dichroism spectroscopy (CD), Fourier transform infrared spectroscopy (FT-IR), and differential scanning calorimetry.

2.1.2 Manufacturing process

The drug substance is produced by solid phase synthesis using the following starting materials: [redacted], and [redacted].

The following were addressed to establish the quality control strategy (Table 1):

- Identification of critical quality attributes (CQAs)
- Identification of critical process parameters (CPPs) based on quality risk assessment and design of experiments

Table 1. Outline of control strategies for the drug substance

CQA	Control method
Content	Specifications
Description	Specifications
Identification	Manufacturing process and specifications
Related substance	Manufacturing process and specifications
Residual solvent	Manufacturing process and specifications
Elemental impurity	Manufacturing process
Water content	Specifications
Microbial limit	Specifications

The peptide synthesis, shredding and purification, [redacted] synthesis, purification, desalting, and lyophilization have been defined as critical steps. [redacted] and [redacted] are controlled as critical intermediates.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content (zilucoplan [HPLC] and sodium [ion chromatography]), description, identification (MS, HPLC), purity (related substances [HPLC], residual solvent [GC]), water content, assay, bacterial endotoxins, and microbial limit.

2.1.4 Stability of drug substance

Table 2 shows the main stability study for the drug substance. The results show that the drug substance is stable. The results of a photostability study indicated that the drug substance is photolabile.

Table 2. Stability study for the drug substance

Study	Primary batch	Temperature	Humidity	Storage form	Storage period
Long-term	3 pilot batches	−20 ± 5°C	—	High-density polyethylene bottle with polypropylene screw cap + multilayer aluminum foil bag	48 months: 1 batch 36 months: 2 batches

Based on the above results, a retest period of 36 months was proposed for the drug substance when stored at −20°C ± 5°C in a high-density polyethylene bottle with polypropylene screw cap packed in a multilayer aluminum foil bag, protected from light.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a solution for injection containing zilucoplan drug substance (40 mg/mL). It is a combination product and supplied as a prefilled glass syringe with a needle, which comes prefilled with the drug solution. The drug product contains the following excipients: sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate anhydrous, sodium chloride, and water for injection.

2.2.2 Manufacturing process

The manufacturing process for the drug product consists of [redacted], [redacted], filtration sterilization, aseptic filling and capping, [redacted], [redacted], assembly and labeling, packaging/storage, and testing/storage.

[redacted], [redacted], filtration sterilization, aseptic filling and capping, [redacted], packaging/storage, and testing/storage have been defined as critical steps. Process control items and values have been established for [redacted], [redacted], filtration sterilization, and aseptic filling and capping steps.

The following matters were addressed to establish the quality control strategy (Table 3):

- Identification of CQAs
- Identification of CPPs based on quality risk assessment and design of experiments

Table 3. Outline of control strategies for the drug product

CQA	Control method
Strength	Specifications
Description	Manufacturing process and specifications
Identification	Specifications
Related substance	Manufacturing process and specifications
Particulate matter	Manufacturing process and specifications
Filled volume	Manufacturing process
Uniformity of dosage units	Manufacturing process and specifications
[redacted]	Specifications
Residual solvent	Manufacturing process
Elemental impurity	Manufacturing process
pH	Specifications
Osmolality	Specifications
Sterility	Manufacturing process and specifications

2.2.3 Control of drug product

The proposed specifications for the drug product consist of strength, description, identification (UV, HPLC), osmolality, pH, purity (related substance [HPLC]), bacterial endotoxins, extractable volume, foreign insoluble matter, insoluble particulate matter, sterility, and assay (HPLC).

2.2.4 Stability of drug product

Table 4 shows the main stability studies on the drug product. The results indicated that the drug product is stable. The results of a photostability study indicated that the drug product is photolabile.

Table 4. Stability studies on the drug product

Study	Primary batch	Temperature	Humidity	Storage form	Storage period
Long-term	3 commercial-scale batches	5 ± 3°C	—	Glass syringe + fluoropolymer-laminated bromobutyl plunger stopper	36 months: 2 batches 24 months: 1 batch
Accelerated	3 commercial-scale batches	25 ± 2°C	60 ± 5% RH		24 months

Based on the above results, a shelf life of 36 months was proposed for the drug product when stored at 2°C to 8°C in a glass syringe with a fluoropolymer-coated bromobutyl plunger stopper as primary packaging, in a paper box protected from light according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q1E Guidelines.

2.R Outline of the review conducted by PMDA

From the submitted data, PMDA concluded that the quality of the drug substance and the drug product is adequately controlled.

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

The results from the studies of primary pharmacodynamics, secondary pharmacodynamics, and safety pharmacology were submitted as the non-clinical pharmacological data. RA102758 and RA103488, the metabolites of zilucoplan,[1)] were also analyzed in some of the studies. Results from the main studies are outlined in this section. Unless otherwise stated, the concentration and dose of zilucoplan sodium are expressed as zilucoplan.

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies

3.1.1.1 Ability to bind to C5

The ability of zilucoplan to bind to human C5 was investigated by surface plasmon resonance (SPR). The mean (± standard deviation) association rate constant (ka), dissociation rate constant (kd), and dissociation constant (K_D) for binding to human C5 were $6.3 \pm 2.5 \times 10^5$ $(mol/L)^{-1}s^{-1}$, $2.1 \pm 1.1 \times 10^{-4}$ s^{-1}, and $4.3 \pm 3.5 \times 10^{-10}$ mol/L,

1) In a monkey study (CTD 4.2.2.4.6), the $AUC_{0\text{-}24h}$ of the metabolites was 8.11% (RA102758) and 18.4% (RA103488) of the $AUC_{0\text{-}24h}$ of unchanged zilucoplan following administration of zilucoplan 0.25 mg/kg, and 31.8% (RA102758) and 5.44% (RA103488) of the $AUC_{0\text{-}24h}$ of unchanged zilucoplan following administration of zilucoplan 10 mg/kg.

respectively (CTD 4.2.1.1.1). An analysis of the co-crystal structure of a zilucoplan peptide analog, RA30303, in complex with C5d, a part of human C5b, by X-ray diffraction revealed binding of RA30303 to C5d (CTD 4.2.1.1.16).

3.1.1.2 Inhibition of complement activation pathway

The inhibition of the classical complement pathway activation by zilucoplan was assessed based on hemolysis of antibody-sensitized sheep erythrocytes exposed to human serum. Zilucoplan blocked hemolysis in normal human serum with a 50% inhibitory concentration (IC_{50}) of 4.9 nmol/L and in C5-depleted normal human serum supplemented with human C5 with an IC_{50} of 2.4 nmol/L. The inhibition of the alternative complement pathway activation was assessed based on hemolysis of rabbit erythrocytes exposed to normal human serum in the absence of Ca^{2+}. Zilucoplan inhibited hemolysis with an IC_{50} of 59.2 nmol/L (CTD 4.2.1.1.3).

An enzyme-linked immunosorbent assay (ELISA) was performed to quantify C5a and sC5b-9, products that formed when antibody-sensitized sheep erythrocytes were exposed to normal human serum. Zilucoplan inhibited the production of C5a and sC5b-9 with IC_{50} values of 4.7 and 5.9 nmol/L, respectively. The inhibition of hemolysis by zilucoplan was also measured simultaneously, with the IC_{50} being 9.6 nmol/L (CTD 4.2.1.1.2).

Inhibition of complement pathways (classical, alternative, and lectin) by zilucoplan was assessed by ELISA. The amount of sC5b-9 formed on the surface of the plate coated with activators for the specific pathway was determined after addition of human serum spiked with zilucoplan to the plate. Zilucoplan inhibited the formation of sC5b-9 for all pathways with IC_{50} values of 11.2 nmol/L, 17.2 nmol/L, and 3.6 nmol/L for classical, alternative, and lectin pathways, respectively (CTD 4.2.1.1.4).

3.1.1.3 Effects on C5b6 complex (CTD 4.2.1.1.17)

Human C5b tends to undergo aggregation unless it binds to C6 to form a stable complex (*J Exp Med.* 1970;132:775-93, *J Biol Chem.* 1983;258:10629-36). After preincubation of zilucoplan with C5b-6 complex, gel electrophoresis was performed to evaluate the effect of zilucoplan on the binding of human C5b and C6. The dissociation of the C5b-6 complex was promoted in the presence of zilucoplan.

3.1.1.4 Inhibition of C5 genetic variants

Published literature has reported that patients with the human C5 p.Arg885His mutation (R885H) or p.Arg885Cys mutation (R885C) poorly responded to eculizumab (genetical recombination; hereinafter referred to as “eculizumab”), a C5 inhibitor (*N Engl J Med.* 2014;370:632-9). The ability of zilucoplan and eculizumab to bind to each type of C5 (human serum C5, recombinant human C5 wild-type, and recombinant human C5 variants [R885H and R885C]) was evaluated by SPR, and the K_D values are shown in Table 5. The inhibition of each type of human C5 by zilucoplan or eculizumab was assessed based on hemolysis of antibody-sensitized sheep erythrocytes exposed to C5-depleted normal human serum supplemented with each type of human C5, and the IC_{50} values are also shown in Table 5.

Table 5. Binding affinity and inhibitory effects of zilucoplan and eculizumab for each type of human C5

Type of human C5	Substance tested	CTD 4.2.1.1.5	CTD 4.2.1.1.6
		K_D (pmol/L)	IC_{50} (nmol/L) for hemolysis
Human serum C5	Zilucoplan	1.19	2.2
	Eculizumab	<0.18	0.7
Recombinant human C5 wild-type	Zilucoplan	40.7	1.4
	Eculizumab	0.21	0.6
Recombinant human C5 variant (R885H)	Zilucoplan	73.6	8.6
	Eculizumab	ND	>4000
Recombinant human C5 variant (R885C)	Zilucoplan	25.5	3.7
	Eculizumab	ND	>4000

ND = Not detected

3.1.1.5 Species specificity (CTD 4.2.1.1.7)

Animal species specificity in the inhibition of classical complement pathway activation by zilucoplan was evaluated based on hemolysis of antibody-sensitized sheep erythrocytes exposed to plasma or serum of different animal species. Zilucoplan inhibited the hemolysis of plasma or serum of different animal species with the IC_{50} values shown in Table 6.

Table 6. Inhibition of hemolysis by zilucoplan in different animal species

Animal	IC_{50} (nmol/L) for hemolysis	Animal	IC_{50} (nmol/L) for hemolysis	Animal	IC_{50} (nmol/L) for hemolysis
Human	7	Rhesus monkey	18	Dog	>4636
Cynomolgus monkey	4	Miniature pig	50	Mouse	>35649
Baboon	5	Swine	113	Rabbit	>66554
Chimpanzee	10	Rat	609	Guinea pig	>100000

3.1.1.6 Comparison of activity between zilucoplan and its metabolites

The inhibition of classical complement pathway activation by zilucoplan, RA102758, and RA103488 was evaluated based on hemolysis of antibody-sensitized sheep erythrocytes exposed to different types of human serum. Table 7 shows the IC_{50} values for hemolysis. While RA102758 had a markedly low inhibitory effect on hemolysis compared to zilucoplan, RA103488 had a similar inhibitory effect to that of zilucoplan. According to the applicant's explanation, because RA103488 is present at lower concentrations than that of zilucoplan in human plasma [see Section 6.2.2.1]; therefore, the contribution of these metabolites to the pharmacodynamic action of zilucoplan in humans is not substantial.

Table 7. Inhibition of hemolysis by zilucoplan and its metabolites

Serum used	Substance tested	IC_{50} (nmol/L) for hemolysis	CTD
Normal human serum	Zilucoplan	4.6	4.2.1.1.8
Normal human serum	RA102758	30884	
Normal human serum	Zilucoplan	5.2	4.2.1.1.9
Normal human serum	RA103488	5.5	
C5-depleted normal human serum supplemented with human C5	Zilucoplan	0.84	
C5-depleted normal human serum supplemented with human C5	RA103488	0.62	

3.1.2 *Ex vivo* studies

3.1.2.1 Inhibition of complement activation pathway in cynomolgus monkeys

Zilucoplan 0.21 or 4.2 mg/kg was administered subcutaneously to male cynomolgus monkeys (N = 2/group) once daily for 7 days, and plasma samples from the animals were used in the analysis. Figure 1 shows the plots

of plasma zilucoplan concentrations and the percent hemolysis (where the hemolysis in plasma samples prior to treatment is 100%; the same applies hereinafter) based on hemolysis assay with antibody-sensitized sheep erythrocytes. Hemolysis was almost completely inhibited from 1 hour after the first dose of zilucoplan until the end of the treatment period, and the percent hemolysis tended to increase over time after the end of treatment. The relationship between plasma zilucoplan concentrations and percent hemolysis was evaluated. The 90% effective concentration (EC_{90}) for hemolysis inhibition by zilucoplan was 2.5 μg/mL (CTD 4.2.2.2.3).

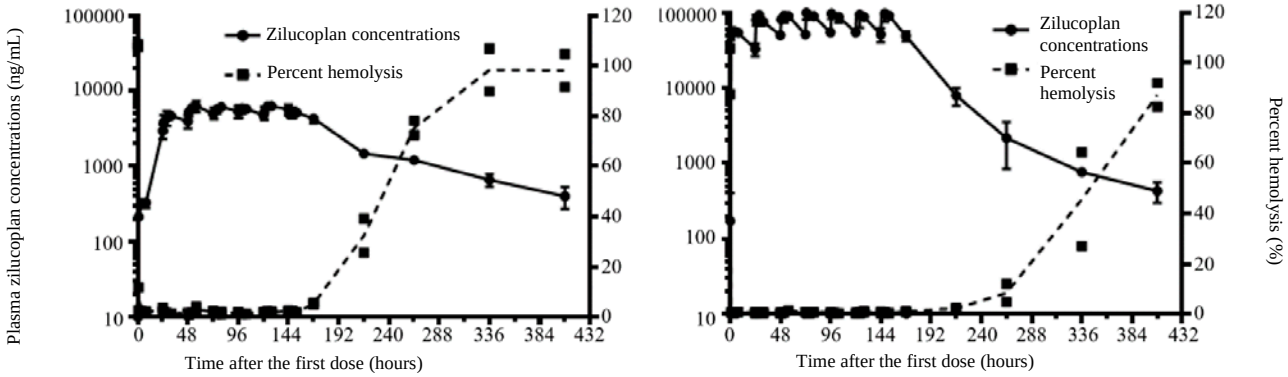


Figure 1. Changes over time in plasma zilucoplan concentrations and percent hemolysis. The zilucoplan 0.21 mg/kg/day group (left); the zilucoplan 4.2 mg/kg/day group (right).

Percent hemolysis was determined based on hemolysis assay with antibody-sensitized sheep erythrocytes, using plasma samples from animals used in the 4-week and 13-week repeated toxicity studies [see Section 5.2]. The percent hemolysis remained <5% at all dose levels (1, 2, and 4 mg/kg/day in the 4-week study; 0.25, 1, 2, and 10 mg/kg/day in the 13-week study) from 2 hours after the first dose of zilucoplan up to 4 or 13 weeks of treatment (CTD 4.2.3.2.2 and 4.2.3.2.3). A similar analysis was performed in the 39-week repeated dose toxicity study [see Section 5.2]. The percent hemolysis from 2 hours after the first dose of zilucoplan up to 39 weeks of treatment was <20% at 0.25 mg/kg/day and <10% in all individual animals at 1, 2, 4, and 6 mg/kg/day except for animals with dose interruptions due to discharge from the eye and reddening (CTD 4.2.3.2.6). In all studies, percent hemolysis returned to around baseline levels after a recovery period (4 or 8 weeks).

3.2 Secondary pharmacodynamics

3.2.1 Binding specificity to proteins in human serum

The binding of zilucoplan to human complement proteins (C3, C4, C5, C6, and C7), C3 subdomain, human serum albumin (HSA), and human carbonic anhydrase II was investigated by SPR. Zilucoplan bound to C5 (K_D = 1.4 nmol/L) and bound weakly to C4 and HSA (K_D, >10 μmol/L). Zilucoplan did not bind to the other proteins (CTD 4.2.1.2.1).

Complement protein C5 is comprised of α- and β-chains, linked by a disulfide bridge. The biotinylated compound with an amino acid sequence identical to that of the core sequence of zilucoplan that recognizes C5 was incubated with normal human serum, and then followed by pull-down with streptavidin bound beads and

sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) under reducing conditions. Only 2 bands corresponding to the molecular weights of the C5α-chain and the β-chain were detected by SDS-PAGE. The band corresponding to the molecular weight of the C5α-chain was confirmed to be the C5α-chain by Western blot using an anti-C5α antibody (CTD 4.2.1.2.2).

3.2.2 Evaluation of activities of zilucoplan and RA102758 at other receptors (CTD 4.2.1.2.3)

Because pancreatic findings were reported in the 4-week and 13-week repeated toxicity studies in cynomolgus monkeys, [see Section 5.2], functional assays of zilucoplan and RA102758 (1.1 to 30 μmol/L for both) were performed, targeting human Cholecystokinin 1 (CCK1), human CCK2, human glucagon, and human secretin receptors. While zilucoplan and RA102758 did not show any activity at ≤10 μmol/L, zilucoplan (30 μmol/L) showed antagonism at CCK2 receptors (mean inhibition of 62.0%) and RA102758 (30 μmol/L) showed antagonism at CCK1 receptors (mean inhibition of 57.4%). According to the applicant's explanation, these activities at the specified receptors are unlikely to pose a problem in clinical practice because the concentrations of zilucoplan and RA102758 at which no activity was showed at the receptors are estimated to be >172 times[2)] the plasma concentrations of zilucoplan and RA102758 in a patient receiving zilucoplan at the clinical dose.

3.2.3 Assessment of activity of zilucoplan and its human metabolites at targets associated with abuse liability

Zilucoplan (30 μmol/L), RA102758 (3 μmol/L), and RA103488 (3 μmol/L) were evaluated for their ability to interact with 35 receptors, transporters, and other targets in binding assays. Zilucoplan inhibited human orexin-1 (OX1) receptor (mean inhibition of 62%) and rat gamma amino butyric acid (GABA) transporter (mean inhibition of 52%), while RA102758 and RA103488 did not inhibit any receptors or targets by >50% (CTD 4.2.1.2.4).

Binding assays showed that zilucoplan bound to the human OX1 receptor and rat GABA transporter, with IC_{50} values of 33 and 11 μmol/L, respectively. A functional assay of zilucoplan at the human OX1 receptor showed that zilucoplan exhibit antagonism at the OX1 receptor with an IC_{50} of 44 μmol/L (CTD 4.2.1.2.5). According to the applicant's explanation, these activities at the specified molecules are unlikely to pose a problem in clinical practice because the IC_{50} for antagonism at the OX1 receptor and the IC_{50} for antagonism at the rat GABA transporter were estimated to be >759 times and >190 times, respectively, [3)] the plasma zilucoplan concentration in a patient receiving zilucoplan at the clinical dose.

2) The estimated zilucoplan exposure (C_{max}) in a patient with 80kg body weight who received zilucoplan 32.4 mg as a subcutaneous injection was 20.7 μg/mL (5.8 μmol/L) and the protein binding of zilucoplan in human plasma was >99% [see Section 6.2.1]. Zilucoplan showed no activity at the receptors for human CCK1, human CCK2, human glucagon, and human secretin at the concentration that was >172 times the unbound concentration of zilucoplan in human plasma. Given that the C_{max} of RA102758 in healthy adults receiving zilucoplan 0.3 mg/kg subcutaneously was lower than that of (unchanged) zilucoplan [see Section 6.2.2.1] and that the protein binding of RA102758 in human plasma was >99% [see Section 6.2.1], it is inferred that the concentrations at which no activity was seen at the above-mentioned receptors would even greater than 172 times the unbound concentration of RA102758 in human plasma.

3) The estimated zilucoplan exposure (C_{max}) in a patient with 80 kg body weight receiving zilucoplan 32.4 mg was 20.7 μg/mL (5.8 μmol/L) and the protein binding of zilucoplan in human plasma was >99% [see Section 6.2.1]. The IC_{50} values for antagonism at the OX1 receptor and for antagonism at the rat GABA transporter were >759 times and >190 times, respectively, the unbound concentration of zilucoplan in human plasma.

3.3 Safety pharmacology

Table 8 summarizes the results of the safety pharmacology study and assessments of the effects on the central nervous system in the 4-week repeated dose toxicity study in cynomolgus monkeys.

Table 8. Summary of data from safety pharmacology evaluation

Organ system	Test system	Test parameter/method	Treatment duration (regimen)	Route of administration	Dose	Finding	Exposure ratio[a)]	CTD
Central nervous system	Cynomolgus monkeys (N = 3/sex/group)	Clinical signs, behavior, motor function, nervous/sensory system function	4 weeks (Once daily)	SC	0,[b)] 1, 2, or 4 mg/kg	No effects	3.10	4.2.3.2.2
Cardiovascular and respiratory systems	HEK293	hERG channel current	*In vitro*		300 µmol/L	39.2% increase	>51.7	4.2.1.3.1
	Cynomolgus monkeys (N = 4 males/group)	Clinical signs, electrocardiography, arterial blood pressure, respiratory parameters (respiratory rate, tidal volume, and minute ventilation)	Single dose	SC	0,[b)] 2, or 10 mg/kg[c)]	No effects	3.82	4.2.1.3.2

HEK293, human embryonic kidney cells 293; hERG, human ether-à-go-go-related gene

a) The exposure (C_{max}) or concentrations studied (unbound form) (*in vitro* study) at the highest dose that showed no findings (*in vivo* study) were compared to the estimated zilucoplan exposure (C_{max}, 20.7 µg/mL) in a patient with 80 kg body weight receiving zilucoplan 32.4 mg.

b) Vehicle: 50 mmol/L sodium phosphate, 0.9% sodium chloride, pH 7.0

c) Vehicle was administered on Day 1 and zilucoplan 2 or 10 mg/kg on Day 8.

3.R Outline of the review conducted by PMDA

3.R.1 Primary pharmacodynamics

The applicant's explanation about the effects of zilucoplan on gMG:

Myasthenia gravis is an autoimmune disease mediated by autoantibodies against acetylcholine receptors (AChRs), muscle-specific receptor tyrosine kinase (MuSK), and other molecules on the postsynaptic membrane at the neuromuscular junction. Of Japanese patients with MG, approximately 80% to 85% are anti-AChR-antibody positive, and approximately 5% are anti-MuSK-antibody positive (*Japanese Clinical Guidelines 2022 for Myasthenia Gravis and Lambert-Eaton Myasthenic Syndrome*. [in Japanese] ed. Japanese Committee of Clinical Guidelines for MG; hereinafter referred to as "MG Clinical Guidelines"). The pathogenesis of the disease in patients with anti-AChR-antibody positive gMG is considered as follows: The anti-AChR antibodies, consisting primarily of IgG1 and IgG3 subclasses, bind to AChR, which activates the complement pathway, leading to deposition of the terminal product of the complement activation pathway, the membrane attack complex (sC5b-9), on the postsynaptic membrane at the neuromuscular junction, damaging the neuromuscular junction, thereby disrupting neurotransmission (*Ann NY Acad Sci.* 2018;1412:113-28). In contrast, anti-MuSK-antibodies are mainly composed of the IgG4 subclass, which does not activate the complement pathway, suggesting that MG is caused by a mechanism not mediated by the complement system in patients with anti-MuSK-antibody positive gMG (*J Autoimmun.* 2017;77:104-15, *Ann NY Acad Sci.* 2018;1413:111-8).

The submitted data include the *in vitro* and *ex vivo* studies, which show that zilucoplan binds to C5 and C5b to inhibit the cleavage of C5 into C5a and C5b, and also blocks the binding of C5b to C6. In light of the pathogenesis of gMG mentioned above, zilucoplan acts by inhibiting membrane attack complex formation at

the neuromuscular junction in patients with anti-AChR-antibody positive gMG, thereby reducing damage at the neuromuscular junction and disruption of neurotransmission.

Zilucoplan showed binding affinity for C5 variants (R885H or R885C), which are reported to reduce the effect of eculizumab, and inhibited hemolysis mediated by C5 variants (R885H or R885C), indicating that zilucoplan is expected to be effective in patients with gMG carrying C5 variants (R885H or R885C). The clinical studies (Studies UP0113, MG0009, and MG0010) included no subjects carrying genetic mutations of C5 R885 (R885H or R885C).

PMDA's view:
In light of the data submitted and the pathogenesis of gMG, zilucoplan is expected to be effective in the treatment of patients with anti-AChR-antibody positive gMG because it binds to C5 and C5b to inhibit the cleavage of C5 into C5a and C5b, and also blocks the binding of C5b to C6. In addition, zilucoplan showed binding affinity for C5 variants (R885H or R885C), and inhibited hemolysis mediated by C5 variants (R885H or R885C), indicating that zilucoplan is expected to be effective in patients with anti-AChR-antibody positive gMG carrying C5 variants (R885H or R885C).

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

The applicant submitted data from non-clinical pharmacokinetic studies in rats and monkeys for the evaluation of absorption, distribution, metabolism, and excretion of zilucoplan. The concentrations of zilucoplan in biological samples were determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS) (lower limit of quantitation [LLOQ] = 100 or 1250 ng/mL). Radioactivity levels in biological samples in studies that used ^{14}C-radiolabeled zilucoplan were measured by liquid scintillation counter (LLOQ = 0.0118 or 0.0218 μg eq/g). The levels of anti-zilucoplan antibodies in serum were measured by ELISA (LLOQ = 0.60 ng/mL). Unless otherwise specified, t_{max} is expressed as the median, and the rest of the pharmacokinetic parameters are expressed as the mean or mean ± standard deviation. Only results of the main non-clinical pharmacokinetic studies are presented in the following sections.

4.1 Absorption

4.1.1 Single-dose studies

Table 9 shows the pharmacokinetic parameters of zilucoplan in plasma following administration of a single intravenous or subcutaneous dose of zilucoplan to male rats or male monkeys (CTD 4.2.2.2.1, 4.2.2.2.2, and 4.2.2.2.3). The bioavailability of a single subcutaneous dose of 0.4 mg/kg in 2 monkeys was 71.6% and 74.5%.

Table 9. Pharmacokinetic parameters of zilucoplan in plasma after a single intravenous or subcutaneous dose of zilucoplan

Animal	Route of administration	Dose (mg/kg)	N/group	C_{max} (μg/mL)	t_{max}[a] (h)	$AUC_{0-\infty}$ (μg·h/mL)	$t_{1/2}$ (h)	Vd (mL/kg)	CL (mL/h/kg)	CTD
Rat	IV	2	4	47.40 ± 2.69	0.083 [0.083, 0.083]	379.00 ± 13.10	—	64.3 ± 2.92	5.28 ± 0.181	4.2.2.2.1
	SC	1	3	5.30 ± 1.02	4.00 [2.00, 8.00]	99.22 ± 4.79	9.54 ± 1.23	—	—	4.2.2.2.2
		10	3	45.57 ± 3.75	4.00 [4.00, 8.00]	988.53 ± 50.76	9.27 ± 0.8	—	—	
Monkey	IV	0.4	2	—	—	599.29, 603.49	154, 211	144, 183	0.011, 0.011	4.2.2.2.3
		0.5	2	—	—	1038.0, 1335.62	91.7, 136	58.5, 68.2	0.006, 0.008	
	SC	0.4	2	2.45, 2.53	8.00, 8.00	430.45, 447.93	166, 189	—	—	
		0.5	2	7.26, 9.39	8.00, 24.0	832.04, 1036.14	63.7, 65.8	—	—	

Mean ± standard deviation or individual value; "—," Not applicable or not calculated
a) Median [Min, Max] or individual value

4.1.2 Repeated-dose studies

The toxicokinetics of zilucoplan was investigated in a 4-week repeated subcutaneous dose toxicity study in rats and a 39-week repeated subcutaneous dose toxicity study in monkeys. Table 10 shows the pharmacokinetic parameters of zilucoplan in plasma (CTD 4.2.3.2.1 and 4.2.3.2.6). In the repeated subcutaneous dose toxicity studies lasting 4 weeks, 13 weeks [see Section 5.2], and 39 weeks, anti-zilucoplan antibodies were measured. Anti-zilucoplan antibodies were detected in 1 animal in the 4 mg/kg/day group in the 4-week repeated-dose toxicity study and 1 animal in the 0.25 mg/kg/day group in the 13-week repeated-dose toxicity study, but were not detected in any group in the 39-week repeated-dose toxicity study (CTD 4.2.3.2.2, 4.2.3.2.3, and 4.2.3.2.6).

Table 10. Pharmacokinetic parameters of zilucoplan in plasma after repeated subcutaneous doses of zilucoplan once daily

Animal	Timepoint	Dose (mg/kg)	Sex (N)	C_{max} (μg/mL)	t_{max} (h)[a]	AUC_{0-24} (μg·h/mL)	CTD
Rat[b]	Day 1	2.5	M (3/timepoint)	11.10	4	167.00	4.2.3.2.1
			F (3/timepoint)	7.93	4	133.00	
		10	M (3/timepoint)	38.90	4	647.00	
			F (3/timepoint)	36.00	8	588.00	
		40	M (3/timepoint)	108.00	12	1960.00	
			F (3/timepoint)	73.00	8	1320.00	
	Day 28	2.5	M (3/timepoint)	16.30	4	266.00	
			F (3/timepoint)	15.10	8	274.00	
		10	M (3/timepoint)	54.40	4	1030.00	
			F (3/timepoint)	64.80	4	1100.00	
		40	M (3/timepoint)	157.00	8	3060.00	
			F (3/timepoint)	186.00	12	3950.00	
Monkey	Day 1	0.25	M (3)	3.10 ± 0.35	4 [2, 4]	59.70 ± 1.27	4.2.3.2.6
			F (3)	3.14 ± 0.14	2 [2, 2]	60.20 ± 7.15	
		1	M (3)	12.200 ± 0.53	2 [2, 2]	193.00 ± 6.66	
			F (3)	12.20 ± 1.70	2 [2, 4]	185.00 ± 5.57	
		2	M (5)	21.40 ± 1.90	2 [2, 4]	348.00 ± 22.50	
			F (5)	23.60 ± 2.03	2 [2, 2]	360.00 ± 21.50	
		4	M (5)	37.70 ± 2.13	4 [2, 4]	632.00 ± 41.50	
			F (5)	42.70 ± 2.65	4 [2, 4]	688.00 ± 29.60	
		6	M (5)	66.30 ± 3.85	4 [2, 4]	1110.00 ± 66.10	
			F (5)	63.00 ± 9.04	4 [2, 4]	1040.00 ± 60.90	
	Day 273	0.25	M (4)	5.65 ± 0.81	2 [2, 4]	109.00 ± 14.80	
			F (2)	5.80, 6.17[c]	2, 4[c]	95.80, 120.00[c]	
		1	M (4)	17.60 ± 0.60	2 [2, 4]	306.00 ± 26.90	
			F (4)	17.90 ± 1.50	2 [2, 2]	289.00 ± 42.90	
		2	M (5)	30.60 ± 1.97	2 [2, 2]	534.00 ± 54.20	
			F (5)	33.90 ± 3.92	2 [2, 2]	548.00 ± 68.40	
		4	M (5)	64.90 ± 5.55	3 [2, 4]	1170.00 ± 105.00	
			F (5)	74.80 ± 13.60	4 [2, 4]	1290.00 ± 268.00	
		6	M (5)	100.00 ± 16.00	4 [2, 4]	1890.00 ± 317.00	
			F (3)	91.00 ± 5.09	4 [2, 4]	1610.00 ± 273.00	

Mean or mean ± standard deviation
a) Median or median [Min, Max]
b) Parameters were calculated based on the mean plasma concentration for each timepoint.
c) Individual value

4.2 Distribution

4.2.1 Tissue distribution

A single subcutaneous dose of 6 mg of ^{14}C-radiolabeled zilucoplan (^{14}C-radiolabeled palmitoyl side chain or ^{14}C-radiolabeled terminal lysine residue) was administered to pigmented rats (N = 1 male/timepoint) to investigate the tissue distribution of radioactivity up to 8 weeks post-dose by quantitative whole-body autoradiography. Radioactivity was distributed widely across the tissues after subcutaneous administration, and tissue radioactivity levels peaked at 4 to 8 hours post-dose in many of the tissues studied[4)] and in most tissues by 24 hours post-dose, except for some tissues.[5)] Elimination of radioactivity from the tissues was slow. Radioactivity was detected in approximately half of the tissues studied 8 weeks post-dose.[6)] In the study using a ^{14}C-radiolabeled palmitoyl side chain, the maximum radioactivity level in the renal cortex was higher than that in plasma, and an AUC_{0-t} higher than that in plasma was detected in the following tissues: the renal cortex, white adipose tissue, kidney, brown adipocytes, adrenal cortex, adrenal gland, adrenal medulla, thyroid gland, renal medulla, seminal vesicle, salivary gland, pancreas, and pituitary gland. In the study using a ^{14}C-radiolabeled terminal lysine residue, the maximum radioactivity level exceeding that in plasma was detected in the renal cortex, kidney, urinary bladder wall, and renal medulla, while an AUC_{0-t} exceeding that in plasma was detected in the renal cortex, kidney, renal medulla, liver, thyroid gland, spleen, and adrenal gland. In both studies, radioactivity levels and AUC in the central nervous system tissues were lower than those in other tissues except for the lens (CTD 4.2.2.3.5 and 4.2.2.3.6).

4.2.2 Protein binding

Unchanged zilucoplan at 5 to 10 μmol/L was added to rat or monkey plasma and plasma protein binding was determined by equilibrium dialysis. The protein binding in rat or monkey plasma was >99.9% irrespective of the concentration of unchanged zilucoplan.

Unchanged zilucoplan, RA102758, or RA103488 at 1 μmol/L was added to rat or monkey plasma and plasma protein binding was determined by equilibrium dialysis. The mean protein binding of unchanged zilucoplan was 99.9% in both plasma samples, while the mean protein binding of RA102758 was 99.9% (rats) and 99.8% (monkeys) and that of RA103488 was 99.6% (rats) and 99.1% (monkeys) (CTD 4.2.2.3.3).

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4) Plasma, whole blood, aorta, heart blood, brain (whole), spinal cord, eyeball, lens, uvea, unpigmented skin, pigmented skin, adrenal cortex, adrenal gland, adrenal medulla, pituitary gland, thyroid gland, brown adipose tissue, white adipose tissue, cecum mucosa, esophageal wall, large intestine wall, oral mucosa, small intestine wall, stomach wall (gland), stomach wall (non-glandular), cecum contents, large intestine contents, small intestine contents, stomach contents, urinary bladder contents, bone marrow, lymph node, spleen, thymus, bile (studied only for the ^{14}C-radiolabeled terminal lysine residue), kidney, renal cortex, renal medulla, liver, urinary bladder wall, heart, skeletal muscle, epididymis, preputial gland (studied only for the ^{14}C-radiolabeled terminal lysine residue), prostate, seminal vesicle, testis, lung, nasal turbinate, trachea, exorbital lacrimal gland, Harderian gland, intraorbital lacrimal gland, pancreas, salivary gland, femur

5) In the study using the ^{14}C-radiolabeled palmitoyl side chain, the radioactivity level in the spinal cord peaked at 72 hours post-dose. In the study using the ^{14}C-radiolabeled terminal lysine residue, the radioactivity levels peaked at 72 hours post-dose in the kidney and the renal cortex, and at 672 hours post-dose in the lens.

6) Radioactivity was detected in the following tissues after 8 weeks post-dose:
whole blood, aorta, eyeball, uvea, unpigmented skin, pigmented skin, adrenal gland, adrenal medulla, thyroid gland, stomach wall (non-glandular), spleen, kidney, renal cortex, skeletal muscle, epididymis, nasal turbinate, trachea.
Tissues in which radioactivity was detected after 8 weeks post-dose only in the study using a ^{14}C-radiolabeled palmitoyl side chain: brain (whole), spinal cord, adrenal cortex, pituitary gland, brown adipose tissue, white adipose tissue, cecum mucosa, esophageal wall, large intestine wall, stomach wall (gland), bone marrow, lymph node, seminal vesicle, intraorbital lacrimal gland, pancreas, salivary gland.
Tissues in which radioactivity was detected after 8 weeks post-dose only in the study using a ^{14}C-radiolabeled terminal lysine residue: plasma, heart blood, lens, thymus, renal medulla, heart, preputial gland, prostate, lung.

4.2.3 Placental transfer

The *ex vivo* human placenta perfusion model was used to investigate the placental transfer characteristics of zilucoplan and the effect of human C5 protein on the transport of zilucoplan across the placenta. Following the addition of zilucoplan at 10, 20, or 50 μg/mL to the maternal-side perfusate, the fetal transfer rate (defined as the ratio of fetal to maternal perfusate concentrations, expressed as percentage) was 0.5%, 1.0%, and 0.9%, respectively. Following the addition of zilucoplan at 20 μg/mL to the maternal-side perfusate in the presence of human C5 protein (at 64 or 150 μg/mL), the fetal transfer rate was 0.8% irrespective of the concentration of human C5 protein, suggesting that human C5 protein has no impact on the transport of zilucoplan across the placenta (CTD 4.2.2.3.8).

4.3 Metabolism[7)]

4.3.1 *In vitro* metabolism

After the addition of zilucoplan at 1 μmol/L to rat hepatocytes, the sample was incubated at 37°C for 2 hours. The following metabolites formed: RA102758, RA103056, M3578/2, M3322, M2356, M2169, and M1780 (CTD 4.2.2.4.2).

After the addition of ^{14}C-radiolabeled zilucoplan at 1 μmol/L to monkey plasma, the sample was incubated at 37°C for 8 hours. No metabolites were detected. After the addition of ^{14}C-radiolabeled zilucoplan at 1 or 10 μmol/L to monkey hepatocytes, the sample was incubated at 37°C for 4 hours. Metabolites RA103056 and RA102758 formed, and hydrolyzed products (M1780, M2040, M2169, and M2356) were detected at different peptide binding sites (CTD 4.2.2.4.1).

4.3.2 *In vivo* metabolism

A single subcutaneous dose of ^{14}C-radiolabeled zilucoplan (^{14}C-radiolabeled palmitoyl side chain) 6 mg/kg was administered to rats (N = 1 male/timepoint). Unchanged zilucoplan (59.5% of total plasma radioactivity) and RA102758 (20.9% of total plasma radioactivity) were predominantly detected in plasma up to 168 hours post-dose. In the urine of rats (N = 3 males/timepoint), unchanged zilucoplan (0.13% of total radioactivity administered), RA102758 (3.32% of total radioactivity administered), a mono-oxidation product of RA102758 (2.79% of total radioactivity administered), and an alanine conjugate of RA102758 (0.17% of total radioactivity administered) were detected up to 96 hours post-dose; and in feces, unchanged zilucoplan (1.79% of total radioactivity administered), RA102758 (6.86% of total radioactivity administered), palmitic acid (1.22% of total radioactivity administered), a mono-oxidation product of RA102758 (1.27% of total radioactivity

7) The following metabolites are described in this section:
RA102758: ethylene glycol (EG)-palmitoyl binding C-terminal lysine residue;
RA103488: ω-hydroxylation product of the palmitoyl tail;
RA103933: ω-oxidation product of RA102758 or hydrolyzed product of RA103488;
RA103056 and M3578/2: hydrolyzed product by ring opening of cyclic peptide;
M3322: de-palmitoylated group;
M2356, M2169, and M1780: hydrolyzed product

administered), and an alanine conjugate of RA102758 (1.11% of total radioactivity administered) were detected up to 96 hours post-dose (CTD 4.2.2.4.4).

Zilucoplan 10 mg/kg was administered to monkeys (N = 3-5/sex) once daily subcutaneously. In plasma samples collected from 8 hours post-dose on Day 14 through 8 hours post-dose on Day 28, unchanged zilucoplan and RA102758 (42.0% of the AUC of unchanged zilucoplan in plasma) were predominantly detected, and other metabolites detected included RA103933 and RA103488 (6.24% and 7.77% of the AUC of unchanged zilucoplan in plasma, respectively) (CTD 4.2.2.4.5).

Zilucoplan 0.25 to 10 mg/kg was administered to monkeys (N = 3/sex) once daily subcutaneously for 91 days. In plasma samples collected up to 24 hours post-dose on Day 91, the ratios of the $AUC_{0\text{-}24h}$ of the predominant metabolites, RA102758 and RA103488, to that of unchanged zilucoplan, expressed as percentage, were 8.11% (RA102758) and 18.4% (RA103488) at zilucoplan 0.25 mg/kg and 31.8% (RA102758) and 5.44% (RA103488) at zilucoplan 10 mg/kg (CTD 4.2.2.4.6).

4.4 Excretion

4.4.1 Urinary, fecal, and biliary excretion

A single subcutaneous dose of ^{14}C-radiolabeled zilucoplan (^{14}C-radiolabeled palmitoyl side chain) 6 mg/kg was administered to rats (3 males). Cumulative excretion of radioactivity in urine and feces up to 168 hours post-dose was 8.59% and 17.4%, respectively, of the dose administered (CTD 4.2.2.3.5).

A single subcutaneous dose of ^{14}C-radiolabeled zilucoplan (^{14}C-radiolabeled terminal lysine residue) 6 mg/kg was administered to rats (3 males). Cumulative excretion of radioactivity in urine and feces up to 288 hours post-dose was 48.83% and 16.46%, respectively, of the dose administered (CTD 4.2.2.3.6).

A single intravenous dose of zilucoplan 3 mg/kg was administered to bile duct cannulated monkeys (2 males). The cumulative excretion of RA102758 (corrected for molecular weight) in bile and urine up to 168 hours post-dose was 3.86% and 2.24%, respectively, of zilucoplan administered (CTD 4.2.2.5.4).

4.4.2 Excretion in breast milk

Excretion of zilucoplan in breast milk has not been studied. The applicant provided the following explanation: Because other peptide therapeutics have been shown to pass into breast milk, zilucoplan may pass into breast milk; however, the amount of zilucoplan entering breast milk is inferred to be small, as zilucoplan is a high molecular weight peptide, which is highly plasma protein-bound and hydrophilic.

4.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the *in vivo* behavior of zilucoplan can be predicted to some extent and non-clinical pharmacokinetic characteristics have been elucidated.

5. Toxicity and Outline of the Review Conducted by PMDA

5.1 Single-dose toxicity

Acute toxicity of zilucoplan was evaluated in a safety pharmacology study in cynomolgus monkeys (CTD 4.2.1.3.2). There were no deaths or systemic toxicity associated with zilucoplan. The approximate lethal dose for subcutaneous zilucoplan as determined by the applicant was >10 mg/kg (Table 11).

Table 11. Summary of the single-dose toxicity study

Test system	Route of administration	Dose (mg/kg)	Major findings	Approximate lethal dose (mg/kg)	CTD
Male cynomolgus monkeys	SC	0,[a] 2, 10	No changes suggestive of acute toxicity	>10	4.2.1.3.2

a) Vehicle: 50 mmol/L sodium phosphate, 0.9% sodium chloride, pH 7.0

5.2 Repeated-dose toxicity

Repeated subcutaneous dose toxicity studies were conducted in rats (4 weeks) and cynomolgus monkeys (4, 13, and 39 weeks) (Table 12). Major findings were as follows: epithelial findings (e.g., erosion of the skin, tongue, vagina, uterine cervix, oral cavity, and other tissues, ulcer, cellular infiltration, vesicle degeneration), lymphocyte hyperplasia (an increase in lymphocytes, an increase in lymphocyte aggregates, an increase in lymphoid follicles), pancreatic findings (e.g., acinar degeneration, pancreatic duct hyperplasia, elevated lipase, elevated amylase), and hepatic findings (e.g., jaundice, hepatic fibrosis, hyperplasia of the bile duct epithelium, pericholangitis, elevated hepatic enzymes). According to the explanation by the applicant, these findings are secondary changes caused by the immunosuppressive effect of zilucoplan.

In the 4-week repeated subcutaneous dose toxicity study in rats, the zilucoplan exposure (mean AUC in male and female animals) at 10 mg/kg, the no-observed adverse effect level (NOAEL), was 1065 μg·h/mL, which was approximately 3.9 times the estimated exposure (AUC, 275 μg·h/mL) in humans at the maximum recommended clinical dose (32.4 mg for patients weighing 80 kg). In the 39-week repeated toxicity study in cynomolgus monkeys, the zilucoplan exposures (mean AUC in male and female animals) at the lowest dose (0.25 mg/kg) and the maximum tolerated dose (2 mg/kg) were 108.5 and 541 μg·h/mL, respectively, which were 0.4 times and 2 times, respectively, the estimated exposure (AUC, 275 μg·h/mL) in humans at the maximum recommended clinical dose (32.4 mg for patients weighing 80 kg).

Table 12. Summary of repeated-dose toxicity studies

Test system	Route of administration	Duration of dosing	Dose (mg/kg/day)	Major findings	NOAEL (mg/kg/day)	CTD
Male/ female rats (SD)	SC[a]	4 weeks + 4-week recovery period	0,[b] 2.5, 10, 40	At ≥2.5 mg/kg/day, reddening at injection site At ≥10 mg/kg/day, scratches/edema/subcutaneous muscle fiber degeneration at injection site, mononuclear cell infiltration/mixed cell infiltration/fibrosis/edema in subcutaneous tissue at injection site At 40 mg/kg/day, swelling/thickening/scabs/dark red foci/subcutaneous tissue abscess formation accompanied by skin surface erosion or ulceration at injection site, a decrease in hemoglobin concentration, an increase in reticulocyte count, an increase in red blood	10	4.2.3.2.1

Test system	Route of administration	Duration of dosing	Dose (mg/kg/day)	Major findings	NOAEL (mg/kg/day)	CTD
				cell volume distribution width, an increase in neutrophil count, an increase in fibrinogen levels Reversibility: reversible		
Male/ female cynomolgus monkeys	SC[c)]	4 weeks + 4-week recovery period[d)]	0,[b)] 1, 2, 4	At ≥1 mg/kg/day, edema, fibroplasia, hemorrhage, muscle cell degeneration/regeneration, subcutaneous mixed cell type inflammation, increase in medullary cell count/an increase in lymphoid follicles in the thymus At ≥2 mg/kg/day, elevated bile acid, elevated lipase, injection site swelling Reversibility: reversible	4	4.2.3.2.2
Male/ female cynomolgus monkeys	SC[c)]	13 weeks + 4-week recovery period[e) f)]	0,[b)] 0.25,[g)] 1,[h)] 2, 10	At ≥0.25 mg/kg/day, an increase in lymphocyte count/lymphoid follicle formation in the thymic medulla, perivascular mononuclear cell infiltration in the tongue and urinary bladder At ≥1 mg/kg/day, degeneration of pancreatic acinar cells, perivascular mononuclear cell infiltration in the pancreas/rectum/stomach At ≥2[i)] mg/kg/day, perivascular mononuclear cell infiltration in the esophagus/salivary gland At 10 mg/kg/day, red/dry face, jaundice, bilateral eye discharge accompanied by periorbital reddening, abdominal pain, elevated AST/ALT/ALP/GGT/total bilirubin/cholesterol/bile acid/ creatinine kinase, a decrease in albumin, a decrease in A/G ratio, vasculitis in the pancreas, pancreatic duct hyperplasia, elevated amylase/lipase, vesicle degeneration/neutrophil inflammation of the tongue mucosa, degeneration/mononuclear cell inflammation of the salivary duct epithelium, perivascular mononuclear cell infiltration in the kidney/thyroid Reversibility: reversible (except for changes in the pancreas, liver, and thymus[j)])	2	4.2.3.2.3
Male/ female cynomolgus monkeys	SC[c)]	39 weeks + 8-week recovery period[k)]	0,[l)] 0.25, 1, 2, 4, 6	Sacrificed moribund at 0.25[m)] (female, 1/3), 4[n) o)] (male, 1/5), and 6 mg/kg/day[n) o)] (female, 1/5) At ≥0.25 mg/kg/day, swelling in the limb/abdomen/tail/penis/eyelid/ injection site, local and whole body skin reddening, injection site reaction,[p)] mononuclear/neutrophil/mixed cell infiltration in multiple organs, vesicle degeneration of the tongue, a decrease in albumin At ≥1 mg/kg/day, vesicle degeneration/squamous metaplasia in the uterine cervix, endometrial degeneration, an increase in follicular lymphocytes in the spleen, an increase in cells/formation of lymphoid follicles in the thymic medulla At ≥2 mg/kg/day, eye discharge,[q)] vesicle degeneration in the esophagus, degeneration of pancreatic acinar cells accompanied by fibrosis/fibroplasia At ≥4 mg/kg/day, erythema in the buccal mucosa[r)]	<0.25	4.2.3.2.6

Test system	Route of administration	Duration of dosing	Dose (mg/kg/day)	Major findings	NOAEL (mg/kg/day)	CTD
				At 6[s)] mg/kg/day, oral ulcer,[r)] vesicle degeneration in the skin/vagina, lymphocyte aggregation/formation of lymphoid follicles in bone marrow Reversibility: reversible (except for esophageal mucosa cell infiltration, squamous metaplasia in the uterine cervix)		

a) Injection sites were rotated among 4 distinct sites during the dosing period.
b) Vehicle: 50 mmol/L sodium phosphate buffer, 0.9% sodium chloride, pH 7.0
c) Injection sites were rotated among 7 distinct sites during the dosing period.
d) In the antidrug antibody (ADA) assay, ADAs were detected in a specimen collected from 1 female animal in the 4 mg/kg/day group on Day 29; however, no marked effects on plasma zilucoplan concentrations or systemic exposure to zilucoplan. No animals tested positive for ADAs in other ADA assays, which were performed at baseline and on Day 57.
e) In the ADA assay, ADAs were detected in a specimen collected from 1 female animal in the 0.25 mg/kg/day group on Day 92, with the zilucoplan exposure comparable to that of other female animals in the 0.25 mg/kg/day group on Day 92. No animals tested positive for ADAs in other ADA assays, which were performed at baseline and on Day 120
f) Intestinal parasites were found in all groups. Polymerase chain reaction (PCR) testing was also performed on feces from the control group, 1 animal of the 0.25 mg/kg/day group, and the 10 mg/kg/day group, and the results revealed the presence of *Entamoeba histolytica* in all the animals.
g) Elevated lipase in 2 animals and elevated ALP/amylase in 1 animal in the 0.25 mg/kg/day group were not considered evidence of toxicity by the applicant because no pathological changes were noted in the liver or the pancreas. In the animals with elevated lipase and the animal with elevated ALP/amylase, *Entamoeba histolytica* (fecal PCR) and alpha hemolytic streptococcus (blood culture) were detected.
h) Elevated GGT in 2 animals and elevated ALP in 1 animal in the 1 mg/kg/day group were not considered evidence of toxicity by the applicant because no pathological changes were noted in the liver.
i) In the 2 mg/kg/day group, elevated lipase (1 animal) and minor mixed cell infiltration in the lung (1 animal) were noted. Elevated lipase was not considered evidence of toxicity by the applicant because the pathological changes in the pancreas were comparable to those in the control group. Since the finding in the lung was an incidental event found in the cynomolgus monkey, the applicant considers it unlikely to be associated with zilucoplan.
j) Necropsy after the recovery period revealed the following findings: in the 10 mg/kg/day group, pancreatic findings (acinar atrophy/mononuclear cell infiltration/pancreatic duct hyperplasia), and hepatic findings (intrahepatic bile duct hyperplasia with portal bridging/oval cell hyperplasia/fibrosis/an increase in hepatocellular glycogen); in the ≥2 mg/kg/day groups, thymic findings (an increase in lymphocyte count/lymphoid follicle formation in the medulla).
k) The ADA assay detected no ADAs in the zilucoplan group.
l) Vehicle: 50 mmol/L sodium phosphate buffer, pH 7.0
m) Sacrificed moribund due to colitis. The applicant considers this is attributable to stress associated with exacerbation of colitis, which had been present before the start of study, based on study data.
n) Sacrificed moribund due to systemic skin erosion and ulcers.
o) Opportunistic pathogens (*Staphylococcus aureus*, beta hemolytic streptococcus, *Pseudomonas* bacteria, and *Enterococcus* bacteria) were isolated from the affected site.
p) Injection site reactions occurred in 1 animal each in the 0.25 mg/kg/day and 6 mg/kg/day groups. The animal (male) in the 0.25 mg/kg/day group had injection site swelling with sanguinopurulent discharge and necrotic area, while the animal (male) in the 6 mg/kg/day group had yellow discharge at the injection site. Antibacterial and analgesic drugs were administered to these animals.
q) Since 1 animal in the 6 mg/kg/day group had eye discharge (bacteria were detected by bacterial culture), erythema, skin findings (scratches on the buttocks and scabs on the chin and lips), antibiotic and analgesic drugs were administered, and doses of zilucoplan were interrupted.
r) Doses of zilucoplan were interrupted in 1 animal (4 mg/kg/day) that developed erythema in the buccal mucosa and 1 animal(6 mg/kg/day) that developed erythema in the buccal mucosa with oral ulcers until these conditions resolved, and then treatment resumed. However, due to recurrence of the above conditions, treatment of the animal in the 6 mg/kg/day group was discontinued.
s) The concentrations of zilucoplan in lacrimal fluid of the animals in the 6 mg/kg/day group represented the pharmacologically active concentration of zilucoplan. The applicant considers that eye discharge and bacterial infection is attributable to the effect of zilucoplan on the complement defense system in the eye mucosa and oral cavity.

5.3 Genotoxicity

The following studies were conducted. The results demonstrated that zilucoplan is not genotoxic (Table 13).

Table 13. Summary of genotoxicity studies

Study type		Test system	S9 (treatment)	Concentration (μg/mL) Dose (mg/kg/day)	Test result	CTD
In vitro	Bacterial reverse mutation assay	*Salmonella* Typhimurium: TA98, TA100, TA1535, and TA1537	− / +	0,[a] 5, 16, 50, 160, 500, 1600, 5000 (μg/plate)	Negative	4.2.3.3.1
		E. coli: WP2*uvrA*				
	Chromosomal aberration assay using cultured mammalian cells	Primary culture of human peripheral blood lymphocytes	− / + (3 hours)	0,[a] 245, 350, 500 (μg/mL)	Negative	4.2.3.3.1
			− (24 hours)		Negative[b]	
In vivo	Micronucleus assay in rodents	Male rats (SD)		Two subcutaneous doses, at 24 hours apart 0,[c] 125, 250, 500 (mg/kg)	Negative	4.2.3.3.2

a) Phosphate-buffered saline
b) At 350 and 500 μg/mL, a significant increase in the number of cells with chromosomal aberration was noted; however, the applicant considered that the change was of no toxicological significance because the values were within the range of historical control data of the laboratory.
c) 50 mmol/L sodium phosphate buffer, 0.51% sodium chloride, pH 7.0

5.4 Carcinogenicity

No carcinogenicity studies of zilucoplan in rodents have been conducted. The weight of evidence (WoE) approach was used to evaluate the carcinogenicity of zilucoplan. The applicant considered that zilucoplan has a low risk for carcinogenicity [see Section 5.R.2].

5.5 Reproductive and developmental toxicity

A study on the effects on male fertility in cynomolgus monkeys and an enhanced pre- and postnatal developmental toxicity study in cynomolgus monkeys, including an embryo-fetal developmental toxicity study, were conducted (Table 14). While male fertility was evaluated in cynomolgus monkeys in the male fertility study above, female fertility was evaluated in cynomolgus monkeys in the repeated subcutaneous dose toxicity studies (4, 13, and 39 weeks). Histopathological examination of male and female reproductive organs indicated no effects of zilucoplan. The applicant therefore concluded that zilucoplan has no effects on fertility. In the enhanced pre- and postnatal developmental toxicity study in cynomolgus monkeys, including a developmental embryo-fetal toxicity study, no effects on embryo, fetuses, or neonates were noted.

The exposure (AUC) at the NOAEL for the development of offspring (4 mg/kg) was 1190 μg·h/mL, which was approximately 4.3 times the estimated exposure (AUC, 275 μg·h/mL) in humans at the maximum recommended clinical dose (32.4 mg for patients weighing 80 kg).

Table 14. Summary of reproductive and developmental toxicity studies

Study type	Test system	Route of administration	Dosing period	Dose (mg/kg/day)	Major finding	NOAEL (mg/kg/day)	CTD
Effects on fertility	Male cynomolgus monkeys	SC	13 weeks	0,[a] 1, 2, 4	No effects on male reproductive organs	Parent animal (fertility): 4	4.2.3.5.1
Enhanced pre- and postnatal developmental toxicity study including embryo-fetal developmental toxicity study[b]	Female cynomolgus monkeys	SC	Embryo-fetal development phase: gestation days 20-100 Enhanced pre- and postnatal development phase: gestation day 20 through parturition	0,[a] 1, 2, 4	Embryo-fetal development phase: 2 mg/kg/day: abortion (1/4)[c] Enhanced pre- and postnatal development phase: Parent animals: no findings of concern F1 offspring: deaths (1/10, 1/10, and 2/10 at 1, 2, and 4 mg/kg/day)[d]	Dam (general toxicity): 4 Development of F1 offspring: 4	4.2.3.5.3

a) Vehicle, 50 mmol/L sodium phosphate buffer, pH 7.0
b) The following examinations were performed for observation of fetuses: body weight and physical measurements by ultrasonography (distance between the coccyx and cranium, between the tip of nose and occipital bone, between the frontal bone and occipital bone; interocular distance; head width; distance between the anus and the genitalia), organ weight measurement, external observation, organ examination, and skeletal examination.
c) The abortion occurred on gestation day 64. During the combined period up to gestation day 100, comprising the embryo-fetal development phase (N = 4/group) and the enhanced pre- and postnatal development phase (N = 16/group), the overall abortion rate was within the range of historical control data. The abortion was considered unrelated to zilucoplan by the applicant.
d) Death of neonates from 1 to 67 days postpartum were reported as follows: 1 of 10 animals at 1 mg/kg/day, 1 of 10 animals at 2 mg/kg/day, and 2 of 10 animals at 4 mg/kg/day. The mortality rate was lower than the control (3 of 12 animals) and within the range of historical control data. These deaths were considered unrelated to zilucoplan by the applicant.

5.6 Local tolerance

The local tolerance of zilucoplan was evaluated based on the data from the 4-week repeated subcutaneous dose toxicity studies in rats (CTD 4.2.3.2.1), and 4-week and 13-week repeated subcutaneous dose toxicity studies in cynomolgus monkeys (CTD 4.2.3.2.2 and 4.2.3.2.3). The applicant considered that the severity of injection site reactions (e.g., erythema, swelling, thickening, and scabs) depends on the dosage and volume of the formulation administered.

5.7 Other toxicity studies

5.7.1 Metabolites

The metabolite of zilucoplan, RA102758, which accounts for >10% of the total exposure of zilucoplan-related substances following multiple doses of zilucoplan in Japanese subjects, was evaluated in the 4-week, 13-week, and 39-week repeated subcutaneous dose toxicity studies in cynomolgus monkeys (CTD 4.2.3.2.2, 4.2.3.2.3, and 4.2.3.2.6), micronucleus assay in rats (CTD 4.2.3.3.2), and enhanced pre- and postnatal developmental toxicity study in cynomolgus monkeys, including a developmental embryo-fetal toxicity study (CTD 4.2.3.5.3).

5.R Outline of the review conducted by PMDA

5.R.1 Reproductive and developmental toxicity

The applicant conducted no reproductive toxicity studies in rodents (fertility and early embryonic development to implantation, and embryo-fetal development studies) to evaluate the toxicity of zilucoplan. According to the explanation by the applicant, the following toxicity data from the studies indicate that zilucoplan has no effect on development or reproduction.

- Assessment of on- and off-target toxicity raised no concerns about reproductive and developmental

toxicity caused by zilucoplan as shown below:

- In the study investigating the effects on male fertility in cynomolgus monkeys, an animal species in which zilucoplan exerts its pharmacological effect, teste results were studied in detail, and there were no findings of concern [see Section 5.5]. In the 4-week repeated subcutaneous dose toxicity study in rats and 4-week, 13-week, and 39-week repeated subcutaneous dose toxicity studies in cynomolgus monkeys, histopathological examinations of male and female reproductive organs indicated no findings of concern regarding male and female reproductive organs [see Section 5.2].
- An enhanced subcutaneous pre- and postnatal developmental toxicity study in cynomolgus monkeys including an embryo-fetal developmental toxicity study was conducted, and results showed no findings of concern.

- The 4 unnatural amino acids, components of zilucoplan, are not considered to be of significant toxicological concern based on the following grounds:
  - No non-clinical data from the secondary pharmacodynamics, safety pharmacology, repeated-dose toxicity, or other studies [see Sections 3.2, 3.3, and 5.2] that had been conducted by the applicant indicated possibility of off-target toxicity.
  - Two of the 4 unnatural amino acids (*tert*-leucine and cyclohexylglycine) have been used in approved peptide therapeutics, while for the other 2 unnatural amino acids (N-methyl-L-aspartic acid and 7-azatryptophan), N-methyl amino acid and tryptophan analogs are known to be contained in many approved peptide therapeutics.
  - The results of an analysis using (quantitative) structure-activity relationship [(Q)SAR] models (Leadscope and DEREK Nexus) triggered no mutagenicity alerts for the 4 unnatural amino acids. Neither zilucoplan nor its metabolites were shown to be genotoxic in the bacterial reverse mutation assay in the presence and absence of S9 fractions that can produce metabolites, chromosomal aberration assay using cultured mammalian cells, and bone marrow micronucleus assay in rodents (rats) [see Section 5.3].

PMDA's view:

Although no reproductive and developmental toxicity studies in rodents (fertility and early embryonic development to implantation, and embryo-fetal development studies) were conducted, zilucoplan is unlikely to induce severe reproductive and developmental toxicity in humans, based on the reports and other data shown below, as well as the applicant's explanation.

- A component of zilucoplan, 7-azatryptophan is an unnatural amino acid. The aza substitution has been used in many pharmaceutical products to enhance binding selectivity of peptides and prolong the duration of action (e.g., *Future Med Chem.* 2011;3:1139-64, *Curr Med Chem.* 2022;29:6336-58). Aza-substituted peptide therapeutics have been approved, and no genotoxicity or teratogenicity has been reported in non-clinical studies that evaluated the peptide therapeutics.
- In a study that evaluated the metabolites in human plasma (CTD 4.2.2.4.8), production of metabolites composed mainly of unnatural amino acid residue of zilucoplan was minimal.
- It has been reported that C5-deficient mice can develop and breed just as the wild-type mice do (*Methods*

Mol Biol. 2000;150:229-47). No adverse effects were reported in the embryo-fetal development study or the study on the effects on pre-and post-natal development including maternal function, which used a surrogate antibody to eculizumab, a C5 inhibitor like zilucoplan.

- The ability of zilucoplan to transfer across the placenta to the fetus is reported as a mean fetal transfer rate (ratio of fetal to maternal perfusate concentrations, expressed as percentage) of 0.5% to 1.0% [see Section 4.2.3].

5.R.2 Carcinogenicity

The applicant's explanation about the carcinogenicity of zilucoplan:

No carcinogenicity studies of zilucoplan in rodents have been conducted, and the WoE approach was used to evaluate the carcinogenicity of zilucoplan for the following reasons:

- The results of a study on animal species specificity in the inhibition of classical complement pathway activation by zilucoplan [see Section 3.1.1.5] showed that zilucoplan is not pharmacologically active in mice and has extremely low pharmacological activity in rats (1/87 of that in humans), indicating that rodents are not suitable for evaluation of the pharmacological activity of zilucoplan.
- The half-life of zilucoplan is short in rats (9.27 to 9.54 hours), which means that high doses of zilucoplan are required to achieve a certain degree of systemic exposure in rats. However, in the 4-week repeated subcutaneous dose toxicity study in rats, the zilucoplan exposure (mean AUC in male and female animals) at the highest dose (40 mg/kg/day) was 3505 μg·h/mL, which was approximately 12.7 times the estimated exposure in humans at the maximum recommended clinical dose, and serious skin toxicity was noted. It is difficult to conduct a carcinogenicity study in rats at doses higher than the human exposure because (1) serious skin toxicity was noted at 40 mg/kg; (2) serious skin toxicity was not observed at 10 mg/kg in the 4-week study but adverse effects are likely to occur in a long-term study; and (3) the exposures to zilucoplan at 40 mg/kg/day and 10 mg/kg/day in rats were approximately 12.7 times and 3.9 times the human exposure, respectively [see Section 5.2]. Further, skin toxicity is likely to occur in mice because the skin morphology and physiology in mice are similar to those in rats.

The following issues were assessed using the WoE approach, and the results suggest that zilucoplan has a low risk for carcinogenicity.

- There are no data suggestive of increased risk for malignancy in C5 knockout mice (*Methods Mol Biol.* 2000;150:229-47) or in patients with congenital C5 deficiency (e.g., *Mol Immunol.* 2015;64:170-6, *J Clin Immunol.* 2013;33:871-5). In addition, there is no clear concern about the risk of malignancy in humans treated with eculizumab or ravulizumab (C5 inhibitor).
- No toxicological findings indicative of off-target toxicity have been reported in the secondary pharmacodynamics, safety pharmacology, repeated-dose toxicity, reproductive and developmental toxicity studies for zilucoplan and its metabolites or other studies [see Sections 3.2, 3.3, 5.2, and 5.5].
- In the 4-week, 13-week, and 39-week repeated subcutaneous dose toxicity studies in cynomolgus monkeys, the immunosuppressive effects caused by zilucoplan and their secondary infections have been reported [see Section 5.2]. However, these findings do not suggest that the incidence of infections increases in

association with elevated risk for specific malignancy, based on the following grounds:

- In the 4-week repeated subcutaneous dose toxicity study in rats, no zilucoplan-associated changes were noted in the thymus, bone marrow, spleen, or other tissues, nor were any signs of systemic infection observed. Conversely, in the 4-week, 13-week, and 39-week repeated subcutaneous dose toxicity studies in cynomolgus monkeys, immunosuppression caused by the pharmacological effect of zilucoplan as well as its accompanying effects on organs arising from the reactivation of latent pathogens and opportunistic infections were noted. However, infections observed in cynomolgus monkeys are unlikely to occur in humans because of differences between humans and monkeys in microbiota in the skin, mucosa, and digestive tract, immune status, hygiene/grooming behavior, and environment.
- While increased *Neisseria* infections have been reported, no increases in the incidence of fungal, parasite, or viral infections in patients with C5 deficiency have been reported (e.g., *Mol Immunol.* 2011;48:1643-55, *Front Microbiol.* 2017;8:1117). The reports and other data do not suggest that C5 inhibition by zilucoplan increases the incidence of infections associated with elevated risk for specific malignancy.
- In the clinical studies, subjects were vaccinated with meningococcal vaccine prior to administration of zilucoplan. As a consequence, no subjects had *Neisseria* infections. The incidence of serious infections in the zilucoplan group was similar to that in the placebo group [see Section 7.R.3.2.2].

- The submitted data have demonstrated that zilucoplan is not genotoxic [see Section 5.3].
- The enhanced pre- and postnatal developmental toxicity study in cynomolgus monkeys, including an embryo-fetal developmental toxicity study, assessments of the effect of zilucoplan on male fertility in cynomolgus monkeys, and histopathological examinations of male and female reproductive organs in the 4-week, 13-week, and 39-week repeated subcutaneous dose toxicity studies in cynomolgus monkeys revealed no findings of concern, suggesting that there are no endocrine disruption effects associated with the use of zilucoplan.

PMDA's view:

Zilucoplan has an immunosuppressive effect mediated by inhibition of C5. In view of the fact that serious infections associated with immunosuppression occurred in cynomolgus monkeys after repeated subcutaneous doses of zilucoplan, the non-clinical data indicate that zilucoplan has an immunosuppressive effect, a factor that raises concerns about carcinogenicity. The development of malignancy associated with the use of zilucoplan in clinical settings will be discussed in Section 7.R.3 based on the data from clinical studies.

5.R.3 Findings in repeated-dose toxicity studies in cynomolgus monkeys

The applicant's explanation about the epithelial, pancreatic, and hepatic findings identified in the repeated-dose toxicity studies in cynomolgus monkeys:

The immunosuppressive effect of zilucoplan contributed to the proliferation of opportunistic pathogens on the epithelial surface that were colonized by host microorganisms, leading to the development of epithelial changes such as mucocutaneous infections, erosion, and ulcers on the skin, tongue, vagina, uterus cervix, oral cavity,

and other tissues. The epithelial changes allowed penetration of pathogens into the epithelium and their spread to organs in the body, recruiting immune cells to eliminate infections, which was considered to be the cause of the findings in the pancreas (e.g., acinar degeneration, pancreatic duct hyperplasia) and the liver (e.g., jaundice, hepatic fibrosis). These findings in monkeys are irrelevant to humans because (1) all the findings are considered secondary changes caused by infections, and (2) microbiota in the skin, mucosa, and digestive tract, immune status, hygiene/grooming behavior, and environment differ between monkeys and humans. The findings above were not observed in a study conducted at a different test laboratory from the one where the repeated toxicity studies of zilucoplan were performed in cynomolgus monkeys. Therefore, all findings are considered to be changes related to the environment of the test laboratory and microbiological factors, in addition to immunosuppression as a pharmacological effect of zilucoplan.

PMDA's view:
The applicant claimed that the epithelial, pancreatic, and hepatic findings observed in cynomolgus monkeys are secondary changes associated with opportunistic infections, but such presumption is not necessarily true, and the findings were potentially due to the direct effects of zilucoplan. Therefore, the risk for the development of epithelial, pancreatic, and hepatic events associated with the use of zilucoplan in clinical settings will be discussed in Section 7.R.3 based on the clinical study results. The opportunistic infections observed in cynomolgus monkeys are attributable to immunosuppression mediated by inhibition of C5. The risk for the development of infections associated with the use of zilucoplan in clinical practice will also be discussed in Section 7.R.3 based on the clinical study results.

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

6.1 Summary of biopharmaceutic studies and associated analytical methods

The concentrations of unchanged zilucoplan and metabolites (RA102758 and RA103488) in biological samples were determined by LC-MS/MS (LLOQ = 10 ng/mL). Binding antibodies against zilucoplan or polyethylene glycol (PEG) were measured by electrochemiluminescence (ECL). The neutralizing activity of the binding antibody was not evaluated.

Unless otherwise specified, the dose of zilucoplan sodium is expressed as zilucoplan

The vial formulation and prefilled syringe formulations (16.6 mg, 23.0 mg, and 32.4 mg) were used in the clinical studies of zilucoplan. The prefilled syringe formulations (16.6 mg, 23.0 mg, and 32.4 mg), which are the formulations to be marketed in Japan, were used in the global phase III studies (Studies MG0010 and MG0011) as the main clinical studies.

6.1.1 Foreign clinical study that investigated pharmacokinetics by injection site (reference study, CTD 5.3.3.1.3, UP0115)

A single dose of zilucoplan was administered to healthy adults (N = 15 for pharmacokinetic evaluation) by subcutaneous injection into areas of the abdomen and upper arm, or the abdomen and thigh using a crossover design to investigate the pharmacokinetics by injection site. The dosage of zilucoplan was 16.6 mg (subjects weighing ≥50 kg and <56 kg), 23.0 mg (subjects weighing ≥56 kg and <77 kg), and 32.4 mg (subjects weighing ≥77 kg and ≤120 kg). The tables below show the pharmacokinetic parameters of zilucoplan injected into the abdomen or upper arm (Table 15) and the abdomen or thigh (Table 16). The results were similar regardless of the injection site.

Table 15. Pharmacokinetic parameters following a single dose of zilucoplan by subcutaneous injection into the abdomen or upper arm

Injection site	N	C_{max} (μg/mL)	AUC_{0-t} (μg·h/mL)	Geometric mean ratio [90% confidence interval (CI)] (upper arm/abdomen)	
				C_{max}	AUC_{0-t}
Abdomen	7	5.18 (13.12)	821.70 (6.46)	0.9579 [0.8803, 1.042]	0.9776 [0.9260, 1.032]
Upper arm	7	5.19 (17.86)	806.30 (5.32)		

Geometric mean (coefficient of variation, %)

Table 16. Pharmacokinetic parameters following a single dose of zilucoplan by subcutaneous injection into the abdomen or thigh

Injection site	N	C_{max} (μg/mL)	AUC_{0-t} (μg·h/mL)	Geometric mean ratio [90% CI] (thigh/abdomen)	
				C_{max}	AUC_{0-t}
Abdomen	8	5.91 (18.26)	903.40 (16.11)	0.8642 [0.8017, 0.9316]	0.9700 [0.9347, 1.007]
Thigh	8	5.103 (14.70)	876.30 (16.20)		

Geometric mean (coefficient of variation, %)

6.2 Clinical pharmacology

6.2.1 Studies using human biomaterials

(1) Plasma protein binding

Unchanged zilucoplan at a concentration of 10 or 100 μmol/L was added to human plasma. The plasma protein binding of zilucoplan was determined by equilibrium dialysis. Zilucoplan was >99.9% protein bound in human plasma at all concentrations (CTD 4.2.2.3.2).

Unchanged zilucoplan or its metabolites, RA102758 or RA103488, at a concentration of 1 μmol/L was added to human plasma, and the unbound fraction was determined by the *EScalate* Equilibrium Shift Assay.[8)] The unbound fraction was 0.17%, 0.14%, and 0.66% for unchanged zilucoplan, RA102758, and RA103488, respectively (CTD 4.2.2.3.3).

(2) Investigation of metabolites in humans

Human hepatocytes were spiked with zilucoplan and incubated for 4 hours. The substances predominantly detected in the samples spiked with zilucoplan at 1 μmol/L were RA102758 (28.1%), M2169/1 (27.2%), and unchanged zilucoplan (18.6%). The substance predominantly detected in the samples spiked with zilucoplan

8) The shift of the binding equilibrium of zilucoplan or the metabolite to human albumin-coated beads following addition of plasma at various dilutions (0.62%-50%) was analyzed. The apparent dissociation constants for binding to human serum albumin on the beads and binding to plasma proteins were calculated from the concentration-dependent shift, and the fraction not bound to plasma proteins was calculated from the dissociation constant.

at 10 μmol/L were unchanged zilucoplan (64.9%), and other metabolites detected were M2169/1 (10.8%), RA102758 (7.2%), and M2356/1 (5.0%) (CTD 4.2.2.4.1).

(3) Metabolism by P450

Human liver microsomes and zilucoplan were incubated at 37°C in the presence of nicotinamide adenine dinucleotide phosphate (NADPH) for 2 hours, and RA103488 was detected in the resulting mixture. Recombinant expression systems for human cytochrome P450 (CYP) isoforms were incubated with zilucoplan for 2 hours and P450 isoforms involved in the formation of RA103488 were analyzed. The results suggested that primarily CYP4F2, to a lesser degree CYP4A11, CYP4F3A, and CYP4F3B, were involved in the formation of RA103488. In the presence of ketoconazole at a concentration of 10 μmol/L, zilucoplan was incubated with human liver microsomes or the recombinant CYP4F2 expression system for 2 hours. Ketoconazole inhibited the formation of RA103488 by 92.6% and 100%, respectively (CTD 4.2.2.4.3).

(4) Enzyme inhibition and enzyme induction

Inhibition of CYP isoforms in human liver microsomes by zilucoplan (0.137-100 μmol/L) was investigated by using specific substrates[9)] for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, and CYP4F. Zilucoplan inhibited the metabolism of the substrates for CYP1A2 (IC_{50} = 79 μmol/L), CYP2B6 (IC_{50} = 94 μmol/L), and CYP3A (midazolam, IC_{50} = 88 μmol/L). Zilucoplan did not show a clear inhibitory effect (IC_{50} >100 μmol/L) on the other CYP isoforms within the concentrations tested (CTD 4.2.2.6.1 and 4.2.2.6.2).

Inhibition of CYP isoforms in human liver microsomes by RA102758 (0.137-100 μmol/L) was investigated by using specific substrates[9)] for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, and CYP4F. RA102758 inhibited the metabolism of the substrates for CYP1A2 (IC_{50} = 66.6 μmol/L), CYP2B6 (IC_{50} = 57.1 μmol/L), CYP2C8 (IC_{50} = 62.3 μmol/L), CYP2D6 (IC_{50} = 84.3 μmol/L), CYP3A (IC_{50} = 55.8 μmol/L for midazolam and IC_{50} = 62.7 μmol/L for testosterone). Zilucoplan did not show a clear inhibitory effect (IC_{50} >100 μmol/L) on the other CYP isoforms within the concentrations tested (CTD 4.2.2.6.3).

Inhibition of isoforms of recombinant human uridine diphosphate glucuronosyltransferase (UGT) by zilucoplan (0.137-100 μmol/L) was investigated by using specific substrates [10)] for UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15. Zilucoplan inhibited the metabolism of UGT1A1 (IC_{50} = 12 μmol/L) and UGT1A3 (IC_{50} = 48 μmol/L). Zilucoplan did not show a clear inhibitory effect (IC_{50} >100 μmol/L) on the other UGT isoforms within the concentrations tested (CTD 4.2.2.6.1).

The applicant explained that unchanged zilucoplan or RA102758 is unlikely to cause drug interactions through inhibition or induction of CYP isoforms, or inhibition of UGT isoforms in clinical settings, in view of the above

9) The following compounds were used: phenacetin (CYP1A2), bupropion (CYP2B6), amodiaquine (CYP2C8), diclofenac (CYP2C9), *S*-mephenytoin (CYP2C19), bufuralol (CYP2D6), midazolam and testosterone (CYP3A), leukotriene B_4 (CYP4F).

10) The following compounds were used: 7-hydroxy-4-trifluoromethylcoumarin (UGT1A1, UGT1A3, UGT1A6, UGT1A9, UGT2B7, and UGT2B15), trifluoperazine (UGT1A4).

study results and the following data: (i) in Japanese subjects receiving zilucoplan 0.3 mg/kg once daily for 14 days in Study UP0113, the C_{max} on Day 14 was 13.50 μg/mL (3.79 μmol/L) for unchanged zilucoplan and 1.620 μg/mL (0.99 μmol/L) for RA102758; (ii) the maximum a posteriori estimate provided by a population pharmacokinetic (PPK) model for the steady-state C_{max} of unchanged zilucoplan in subjects receiving zilucoplan 0.3 mg/kg in Study MG0010 was 22.00 μg/mL (6.18 μmol/L); and (iii) the unbound fraction of unchanged zilucoplan and RA102758 was 0.01.

(5) Transport by drug transporters

The Madin-Darby canine kidney (MDCK II) cell monolayers expressing human P-glycoprotein (P-gp) were used to evaluate the permeability of zilucoplan (0.1-60 μmol/L). The efflux ratio, the ratio of the apparent permeability coefficient value in the basolateral to apical direction (Papp $_{B→A}$) to that in the apical to basolateral direction (Papp $_{A→B}$), was 0.59 to 0.90. The efflux ratio did not differ clearly from that in human P-gp non-expressing cells (0.42-0.77), suggesting that zilucoplan is not a substrate of P-gp (CTD 4.2.2.6.8).

The HEK293 cells expressing human organic anion transporting polypeptide (OATP)1B1 or OATP1B3 were used to investigate transporter-mediated transport of zilucoplan (0.1-60 μmol/L) and RA102758 (0.106-53.1 μmol/L). The uptake activity did not differ significantly between the transporter-expressing and non-expressing cells within the concentrations studied; therefore, it was shown that zilucoplan and RA102758 are not substrates for OATP1B1 or OATP1B3 (CTD 4.2.2.6.7 and CTD 4.2.2.6.8).

Membrane vesicles were prepared from HEK293 cells expressing human multidrug resistance-associated protein 2 (MRP2) or MRP3. The membrane vesicles were spiked with adenosine triphosphate (ATP) or adenosine monophosphate (AMP) to investigate transporter-mediated transport of zilucoplan (0.1-50 μmol/L). The results showed no difference in the ability to transport zilucoplan regardless of the presence of ATP or AMP, suggesting that zilucoplan is not a substrate for MRP2 or MRP3 (CTD 4.2.2.6.7).

(6) Inhibition of drug transporters

The inhibition of the transport of typical substrates for P-gp or breast cancer resistance protein (BCRP) (digoxin for P-gp and cladribine for BCRP) by zilucoplan (0.412-100 μmol/L) was investigated using Caco-2 cell monolayers or MDCK cell monolayers expressing human BCRP. Zilucoplan inhibited the transport of substrates for BCRP (IC_{50} = 31.7 μmol/L). Zilucoplan did not show a clear inhibitory effect (IC_{50} >100 μmol/L) on P-gp (CTD 4.2.2.6.5) within the range of concentrations studied.

The inhibition of the transport of typical substrates for transporters (estradiol-17-β-glucuronide for OATP1B1 and cholecystokinin octapeptide for OATP1B3) by zilucoplan (0.08-60 μmol/L)[11)] was investigated using HEK293 cells expressing human OATP1B1 or OATP1B3. Zilucoplan inhibited the transport of the substrates for OATP1B1 (IC_{50} = 2.36 μmol/L) and OATP1B3 (IC_{50} = 2.12 μmol/L) (CTD 4.2.2.6.8).

11) After preincubation with zilucoplan at 0.08 to 60 μmol/L, the uptake activity of typical substrates was investigated in the presence of zilucoplan at 0.08 to 60 μmol/L.

The inhibition of the transport of the typical substrate (taurocholic acid) by zilucoplan (0.0032-50 μmol/L) was investigated using Chinese hamster ovary (CHO) cells expressing human sodium taurocholate cotransporting polypeptide (NTCP). Zilucoplan did not show a clear inhibitory effect (IC_{50} >50 μmol/L) within the range of concentrations studied (CTD 4.2.2.6.6).

The inhibition of the transport of typical substrates[12)] for transporters by zilucoplan (5 and 50 μmol/L) was investigated using HEK293 cells expressing human OAT1 and OAT3, CHO cells expressing human organic cation transporter 1 (OCT1) or OCT2, and MDCK II cells expressing multidrug and toxin extrusion 1 (MATE1) or MATE2-K. Zilucoplan did not show a clear inhibitory effect (IC_{50} >50 μmol/L) on the transport of any substrate within the range of concentrations studied (CTD 4.2.2.6.7).

The inhibition of the transport of typical substrates (estradiol-17-β-glucuronide for MRP2 and MRP3, taurocholic acid for bile salt export pump [BSEP]) by zilucoplan (0.0032-50 μmol/L) was investigated using membrane vesicles prepared from the cell membrane of Sf9 cells expressing human MRP2, MRP3, or BSEP. Zilucoplan inhibited the transport of the substrates for MRP2 (IC_{50} = 1.8 μmol/L), MRP3 (IC_{50} = 0.5 μmol/L), and BSEP (IC_{50} = 17.9 μmol/L) (CTD 4.2.2.6.6).

The inhibition of the transport of typical substrates[13)] for transporters by RA102758 (0.023-50 μmol/L) was investigated using membrane vesicles prepared from the cell membrane of HEK293 cells expressing human P-gp, BCRP, or BSEP. While RA102758 inhibited the transport of the substrates for P-gp (IC_{50} = 3.01 μmol/L) and BSEP (IC_{50} = 7.35 μmol/L), it did not show a clear inhibitory effect on BCRP (IC_{50} >50 μmol/L) within the range of concentrations studied (CTD 4.2.2.6.9).

The inhibition of the transport of typical substrates[14)] for transporters by RA102758 (0.023-50 μmol/L) was investigated using HEK293 cells expressing human OATP1B1, OATP1B3, OCT1, and OCT2 and MDCK II cells expressing MATE1. RA102758 inhibited the transport of the substrates for OATP1B1 (IC_{50} = 3.97 μmol/L), OATP1B3 (IC_{50} = 6.58 μmol/L), OCT1 (IC_{50} = 12.49 μmol/L), and MATE1 (IC_{50} = 10.82 μmol/L). Conversely, RA102758 did not show a clear inhibitory effect on the transport of the substrate for OCT2 (IC_{50} >50 μmol/L) within the range of concentrations studied (CTD 4.2.2.6.9).

The inhibition of the transport of typical substrates[15)] for transporters by RA102758 (5.31 and 53.1 μmol/L [for OAT1 and OAT3]; 4 and 40 μmol/L [for MATE2-K]) was investigated using HEK293 cells expressing human OAT1 and OAT3 and MDCK II cells expressing MATE2-K. RA102758 did not show a clear inhibitory effect on the transport of any substrate (IC_{50} >40 μmol/L) within the range of concentrations studied (CTD 4.2.2.6.7).

12) The following compounds were used: *p*-aminohippuric acid (OAT1), estrone-3-sulfate (OAT3), and metformin (OCT1, OCT2, MATE1, and MATE2-K).
13) The following compounds were used: N-methyl quinidine (P-gp), estrone-3-sulfate (BCRP), and taurocholic acid (BSEP).
14) The following compounds were used: estradiol-17-β-glucuronide (OATP1B1), cholecystokinin octapeptide (OATP1B3), and metformin (OCT1, OCT2, and MATE1).
15) The following compounds were used: *p*-aminohippuric acid (OAT1), estrone-3-sulfate (OAT3), and metformin (MATE2-K).

According to the explanation by the applicant, unchanged zilucoplan or RA102758 is unlikely to cause drug interactions through inhibition of transporters in clinical settings, based on the above study results and other data including the following findings: (i) in Japanese subjects receiving zilucoplan 0.3 mg/kg once daily for 14 days in Study UP0113, the C_{max} on Day 14 was 13.50 μg/mL (3.79 μmol/L) for unchanged zilucoplan and 1.62 μg/mL (0.99 μmol/L) for RA102758; (ii) the maximum a posteriori estimate provided by a PPK model for the steady-state C_{max} of unchanged zilucoplan in subjects receiving zilucoplan 0.3 mg/kg in Study MG0010 was 22.00 μg/mL (6.18 μmol/L); and (iii) the unbound fraction of unchanged zilucoplan and RA102758 was 0.01.

6.2.2 Studies in healthy adults

6.2.2.1 Phase I study in healthy Japanese and non-Japanese adults (CTD 5.3.3.1.2, Study UP0113)

A randomized, double-blind, placebo-controlled study was conducted to investigate the pharmacokinetics and other aspects of zilucoplan in healthy Japanese and non-Japanese adults (N = 36 for pharmacokinetic evaluation) [see Section 7.1.1 for the study design].Subjects in the single-dose cohort were to receive a single dose of placebo or zilucoplan 0.1 or 0.3 mg/kg subcutaneously, while subjects in the multiple-dose cohort were to receive placebo or zilucoplan 0.3 mg/kg subcutaneously once daily for 14 days. The plasma pharmacokinetic parameters of unchanged zilucoplan, RA102758, and RA103488 following a single or multiple subcutaneous doses of zilucoplan are shown in Table 17 and Table 18, respectively.

Table 17. Plasma pharmacokinetic parameters of unchanged zilucoplan and its metabolites following a single subcutaneous dose of zilucoplan in healthy Japanese and non-Japanese adults

	Analyte	Dose (mg/kg)	N	C_{max} (μg/mL)	t_{max} [a)] (h)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (μg·h/mL)	$AUC_{0\text{-last}}$ (μg·h/mL)
Japanese	Unchanged zilucoplan	0.1	4	1.58 (14.0)	3.02 [3.00, 6.02]	201 (2.2)	480.00 (12.9)	428.00 (12.5)
		0.3	4	3.77 (5.1)	3.03 [3.00, 3.05]	183 (8.4)	808.00 (9.1)	737.00 (8.6)
	RA102758	0.1	4	0.011[b)]	145[b)]	—	—	—
		0.3	4	0.089 (21.4)	146 [146, 146]	—	—	20.30 (39.4)
	RA103488	0.1	4	0.033 (9.5)	312 [312, 313]	—	—	16.80 (9.9)
		0.3	4	0.135 (29.8)	146 [146, 146]	—	—	60.60 (24.5)
Non-Japanese	Unchanged zilucoplan	0.1	4	1.70 (4.4)	3.00 [3.00, 3.03]	174 (7.4)	439.00 (6.2)	401.00 (4.7)
		0.3	4	3.58 (8.8)	6.01 [3.00, 6.02]	165 (11.8)	653.00 (23.2)	607.00 (21.2)
	RA102758	0.1	4	0.012[b)]	144[b)]	—	—	—
		0.3	4	0.065 (29.9)	143 [143, 167]	—	—	11.90 (44.0)
	RA103488	0.1	4	0.036 (25.0)	228 [143, 313]	—	—	17.30 (27.3)
		0.3	4	0.211 (20.2)	143 [143, 167]	—	—	85.90 (16.3)

Geometric mean (coefficient of variation, %); "—," Not calculated
a) Median [Min, Max]
b) N = 1 (plasma concentrations for the remaining 3 subjects were below the limit of quantification [BLQ])

Table 18. Plasma pharmacokinetic parameters of unchanged zilucoplan and its metabolites following multiple subcutaneous doses of zilucoplan in healthy Japanese and non-Japanese adults

	Analyte	Timepoint	N	C_{max} (μg/mL)	t_{max}[a)] (h)	$t_{1/2}$ (h)	$AUC_{0\text{-}tau}$ (μg·h/mL)
Japanese	Unchanged zilucoplan	Day 1	6	3.89 (17.3)	3.04 [1.00, 6.00]	—	76.60 (13.0)
		Day 14	6	13.30 (14.4)	3.00 [1.00, 3.08]	174 (3.9)	272.00 (14.6)
	RA102758	Day 1	6	0.051 (18.3)	23.7 [23.7, 23.7]	—	0.503 (18.6)
		Day 14	6	1.61 (25.2)	23.0 [1.00, 23.2]	108 (9.3)	34.70 (24.1)
	RA103488	Day 1	6	0.060 (25.3)	23.7 [23.7, 23.7]	—	0.658 (29.4)
		Day 14	6	0.889 (32.5)	14.5 [1.00, 23.2]	288 (6.1)	19.00 (29.1)
Non-Japanese	Unchanged zilucoplan	Day 1	6	4.13 (7.9)	5.99 [3.00, 6.02]	—	81.60 (5.5)
		Day 14	6	12.30 (10.6)	3.00 [3.00, 6.00]	169 (7.2)	259.00 (11.4)
	RA102758	Day 1	6	0.050 (14.9)	23.7 [23.6, 23.9]	—	0.479 (15.9)
		Day 14	6	1.27 (20.6)	13.0 [0.0, 23.0]	92.2 (8.1)	28.10 (20.4)
	RA103488	Day 1	6	0.084 (19.2)	23.7 [23.6, 23.9]	—	0.900 (23.7)
		Day 14	6	1.11 (9.6)	2.02 [0.00, 23.0]	275 (8.7)	24.9 (8.5)

Geometric mean (coefficient of variation, %); "—," Not evaluated
a) Median [Min, Max]

6.2.2.2 Phase I study in healthy non-Japanese adults (reference data, CTD 5.3.3.1.1, Study UP0112)

A double-blind, placebo-controlled study was conducted to investigate the pharmacokinetics, pharmacodynamics, and other aspects of zilucoplan following administration of a single dose or multiple doses of zilucoplan to healthy non-Japanese adults (N = 18 for pharmacokinetic evaluation). Subjects were to receive a single subcutaneous dose of zilucoplan 0.05, 0.1, 0.2, or 0.4 mg/kg, or multiple subcutaneous doses of zilucoplan 0.2 mg/kg once daily for 7 days. The plasma pharmacokinetic parameters of unchanged zilucoplan following a single or multiple subcutaneous doses of zilucoplan are shown in Table 19 and Table 20, respectively.

Table 19. Pharmacokinetic parameters of unchanged zilucoplan in plasma following a single subcutaneous dose of zilucoplan 0.05 to 0.4 mg/kg

Dose (mg/kg)	N	C_{max} (μg/mL)	t_{max}[a)] (h)	$t_{1/2}$ (h)	$AUC_{0\text{-}\infty}$ (μg·h/mL)	CL/F (mL/h/kg)	V_z/F (mL/kg)
0.05	2	1.00, 1.02	3, 6	156, 171	189.00, 193.00	0.259, 0.265	58.3, 65.5
0.1	4	1.54 (13.1)	3 [3, 24]	185.3 (3.4)	405.90 (13.6)	0.2464 (13.6)	65.86 (14.7)
0.2	4	2.96 (10.5)	4.5 [3, 48]	170.7 (14.4)	692.20 (20.4)	0.2889 (20.4)	71.15 (10.2)
0.4	4	5.86 (7.6)	4.6 [3, 6]	155.1 (9.3)	855.90 (14.9)	0.4674 (14.9)	104.6 (11.4)

Geometric mean (coefficient of variation, %)
a) Median [Min, Max]

Table 20. Pharmacokinetic parameters of unchanged zilucoplan in plasma following multiple subcutaneous doses of zilucoplan 0.2 mg/kg once daily

Timepoint	N	C_{max} (μg/mL)	t_{max}[a)] (h)	$t_{1/2}$ (h)	AUC_{tau} (μg·h/mL)	CL/F (mL/h/kg)	V_z/F (mL/kg)
Day 1	4	2.53 (4.0)	3 [3, 6]	—	49.93 (6.5)	—	—
Day 2	4	4.08 (4.4)	3 [3, 6]	—	83.09 (8.2)	—	—
Day 4	4	5.97 (5.4)	6 [3, 6]	—	122.90 (6.4)	—	—
Day 7	4	7.27 (9.5)	3 [3, 6]	161.4 (9.4)	150.90 (8.3)	1.330 (8.3)	308.5 (16.1)

Geometric mean (coefficient of variation, %); "—," Not calculated
a) Median [Min, Max]

6.2.3 Studies in patients with gMG

6.2.3.1 Foreign phase II study (CTD 5.3.5.1.1, Study MG0009)

A randomized, double-blind, placebo-controlled, parallel-group study was conducted to investigate the efficacy, safety, and pharmacokinetics of zilucoplan in patients with gMG who had tested positive for anti-AChR antibodies (N = 43 for pharmacokinetic evaluation). Subjects were to receive placebo or zilucoplan 0.1 or 0.3 mg/kg (Table 38) subcutaneously once daily [see Section 7.2.1 for the details of the study design].

Table 21 shows the plasma concentrations of unchanged zilucoplan and its metabolites (RA102758 and

RA103488) following administration of zilucoplan 0.1 or 0.3 mg/kg once daily in the main portion of the study.

Table 21. Plasma concentrations of unchanged zilucoplan and its metabolites at each timepoint

Timepoint		Unchanged zilucoplan		RA102758		RA103488	
		0.1 mg/kg (N = 15)	0.3 mg/kg (N = 14)	0.1 mg/kg (N = 15)	0.3 mg/kg (N = 14)	0.1 mg/kg (N = 15)	0.3 mg/kg (N = 14)
Day 1	1 hour post-dose	0.443 (242.6)[a)]	2.017 (52.6)	—	—	—	—
	3 hours post-dose	1.632 (28.1)	4.029 (27.8)	—	—	—	—
	6 hours post-dose	1.902 (16.0)[a)]	4.573 (17.3)[b)]	—	—	—	0.016 (243.1)[b)]
Week 1	Pre-dose	4.522 (15.2)[a)]	8.709 (43.8)	0.240 (34.5)[a)]	0.797 (42.6)	0.330 (40.0)[a)]	0.808 (28.1)
Week 2	Pre-dose	4.865 (14.6)	10.091 (17.1)[b)]	0.398 (24.5)	1.407 (33.7)[b)]	0.467 (39.5)	1.107 (24.1)[b)]
Week 4	Pre-dose	5.038 (16.2)[a)]	10.153 (15.6)[c)]	0.349 (192.3)[a)]	1.47 (38.5)[c)]	0.420 (129.1)[a)]	1.167 (22.2)[c)]
Week 8	Pre-dose	5.180 (13.3)	9.913 (19.1)[c)]	0.441 (46.3)	1.34 (40.0)[c)]	0.579 (38.3)	1.220 (16.0)[c)]
Week 12	Pre-dose	5.143 (25.9)	10.134 (18.4)[b)]	0.388 (101.0)	1.39 (34.7)[b)]	0.571 (49.0)	1.271 (25.2)[b)]

Geometric mean, μg/mL (coefficient of variation, %); "—," Not calculated
a) N = 14; b) N = 13; c) N = 12

6.2.3.2 Global phase III study (CTD 5.3.5.1.2, Study MG0010)

A randomized, double-blind, placebo-controlled, parallel-group study was conducted to investigate the efficacy, safety, and pharmacokinetics of zilucoplan in Japanese and non-Japanese patients with gMG who were anti-AChR antibody positive (N = 85 for pharmacokinetic evaluation). Subjects were to receive subcutaneous doses of zilucoplan 0.3 mg/kg (Table 44) once daily [see Section 7.3.1 for the details of the study design].

Table 22 shows the trough concentrations of unchanged zilucoplan in plasma at each timepoint following administration of subcutaneous doses of zilucoplan 0.3 mg/kg once daily.

Table 22. Trough concentrations of unchanged zilucoplan in plasma at each timepoint

Timepoint	N	Trough concentration of unchanged zilucoplan (μg/mL)
Week 1	81	11.43 (21.3)
Week 2	82	12.46 (22.0)
Week 4	79	12.98 (25.6)
Week 8	77	12.43 (24.6)
Week 12	75	12.54 (22.4)

Geometric mean (coefficient of variation, %)

After treatment with zilucoplan, 2 subjects (2.3%) and 8 subjects (9.3%) tested positive for ADA and anti-PEG antibodies, respectively.[16)]

6.2.3.3 Global long-term extension study (CTD 5.3.5.2.1, Study MG0011)

An uncontrolled, open-label study was conducted to investigate the safety, pharmacokinetics, and other aspects of zilucoplan in Japanese and non-Japanese patients with gMG (N = 198 for pharmacokinetic evaluation) who had completed the foreign phase II study (Study MG0009) or global phase III study (Study MG0010). Subjects were to receive zilucoplan 0.3 mg/kg (Table 44) subcutaneously once daily [see Section 7.3.2 for the details of the study design].

Table 23 shows the trough concentrations of unchanged zilucoplan in plasma at each timepoint following administration of subcutaneous doses of zilucoplan 0.3 mg/kg once daily.

16) The subjects who tested positive for ADAs and those who tested positive for anti-PEG antibodies were all non-Japanese patients.

Table 23. Trough concentrations of unchanged zilucoplan in plasma at each timepoint

Timepoint[a)]	Placebo / zilucoplan 0.1 mg/kg / zilucoplan 0.3 mg/kg	Placebo / zilucoplan 0.3 mg/kg	Zilucoplan 0.1 mg/kg / zilucoplan 0.1 mg/kg / zilucoplan 0.3 mg/kg	Zilucoplan 0.3 mg/kg / zilucoplan 0.3 mg/kg
Week 1	4.92 (4.5) (N = 5)	10.75 (24.1) (N = 83)	5.44 (15.8) (N = 12)	12.45 (23.4) (N = 81)
Week 4	5.05 (13.2) (N = 5)	11.84 (28.0) (N = 82)	5.77 (15.9) (N = 10)	12.24 (22.5) (N = 82)
Week 12	5.50 (25.1) (N = 5)	11.50 (35.0) (N = 54)	5.42 (14.8) (N = 11)	12.51 (25.6) (N = 65)
Week 24	7.17 [4.23, 7.61] (N = 3)[b)]	11.15 (53.9) (N = 51)	5.46 (13.8) (N = 11)	11.99 (30.5) (N = 54)
Week 36	5.82 (18.6) (N = 4)	11.09 (57.8) (N = 33)	6.76 (26.0) (N = 12)	12.09 (23.3) (N = 44)
Week 168	10.13 (53.0) (N = 4)	10.98 [8.68, 11.32] (N = 3)[b)]	15.53 (26.8) (N = 8)	8.19 (112.8) (N = 5)

Geometric mean, μg/mL (coefficient of variation, %) (number of subjects evaluated)
a) Weeks in this study (MG0011); b) Median [range]

After treatment with zilucoplan, 0 subjects (placebo / zilucoplan 0.3 mg/kg), 2.5% (2 of 81) of subjects (zilucoplan 0.3 mg/kg / zilucoplan 0.3 mg/kg) developed ADA,[16)] while 1.2% (1 of 84) of subjects (placebo / zilucoplan 0.3 mg/kg) and 9.9% (8 of 81) of subjects (zilucoplan 0.3 mg/kg / zilucoplan 0.3 mg/kg) developed anti-PEG antibodies.[16)] Subjects who had become positive for ADAs or anti-PEG antibodies after entering Study MG0011 were 0 subjects (ADAs) and 2 subjects (anti-PEG antibodies).[17)]

6.2.4 Intrinsic factors

6.2.4.1 Effects of hepatic function (CTD 5.3.3.3.1, Study UP0094)

An open-label, parallel-group study was conducted to evaluate the safety and pharmacokinetics of a single subcutaneous dose of zilucoplan in healthy non-Japanese adults (normal hepatic function; N = 8)[18)] and non-Japanese subjects with moderate hepatic impairment (Child-Pugh class B; N = 8).

Subjects were to receive a single subcutaneous dose of zilucoplan 0.3 mg/kg. Table 24 shows the plasma pharmacokinetic parameters of unchanged zilucoplan and its metabolites after a single subcutaneous dose of zilucoplan.

Table 24. Plasma pharmacokinetic parameters of unchanged zilucoplan and its metabolites in subjects with normal hepatic function and those with moderate hepatic impairment after a single subcutaneous dose of zilucoplan

Analyte	Hepatic function	N	C_{max} (μg/mL)	t_{max}[a)] (h)	$t_{1/2}$ (h)	AUC[b)] (μg·h/mL)	Geometric mean ratio [90% CI][c)]	
							C_{max}	$AUC_{0\text{-last}}$
Unchanged zilucoplan	Normal function	8	5.13 (19.3)	8.0 [2.0, 12]	148.3 (17.5)	787.00 (13.3)	0.95 [0.82, 1.10]	0.76 [0.65, 0.88]
	Moderate impairment	8	4.87 (14.4)	4.0 [3.8, 23]	152.2 (10.7)	594.50 (21.6)		
RA102758	Normal function	8	0.126 (24.4)	83 [71, 120]	93.35 (8.0)[d)]	22.81 (27.5)	1.21 [0.99, 1.48]	1.09 [0.79, 1.50]
	Moderate impairment	8	0.152 (22.1)	96 [72, 120]	66.2, 96.0[e)]	24.83 (46.6)		
RA103488	Normal function	8	0.233 (21.0)	120 [96, 120]	206.84 (31.3)[d)]	103.40 (30.4)	1.16 [0.96, 1.41]	1.22 [1.00, 1.50]
	Moderate impairment	8	0.271 (23.0)	120 [48, 120]	220, 237[e)]	126.60 (12.5)		

Geometric mean (coefficient of variation, %); "—," Not calculated;
a) Median [Min, Max]; b) $AUC_{0\text{-}\infty}$ (unchanged zilucoplan), $AUC_{0\text{-last}}$ (metabolites); c) Hepatic impairment to normal hepatic function ratio for C_{max} or AUC; d) N = 4; e) N = 2 (individual values)

17) Because of the possibility of false positive results produced by the antibody measurement method used in Study MG0009, measurement data of Study MG0009 participants who entered Study MG0011 were excluded from the analysis.
18) Healthy adults matched with subjects with moderate hepatic impairment in terms of age-, sex-, and body mass index (BMI).

6.2.4.2 Effects of renal function (CTD 5.3.3.3.2, Study UP0114)

An open-label, parallel-group study was conducted to evaluate the safety and pharmacokinetics of a single subcutaneous dose of zilucoplan in healthy non-Japanese adults[19] (normal renal function, as defined by creatinine clearance[20] of ≥90 mL/min; N = 8) and non-Japanese subjects with severe renal impairment (creatinine clearance[20] of <30 mL/min; N = 8). Subjects were to receive a single subcutaneous dose of zilucoplan 0.3 mg/kg. Table 25 shows the plasma pharmacokinetic parameters of unchanged zilucoplan and its metabolites after a single subcutaneous dose of zilucoplan.

Table 25. Plasma pharmacokinetic parameters of unchanged zilucoplan and its metabolites in subjects with normal renal function and those with severe renal impairment after a single subcutaneous dose of zilucoplan

Analyte	Renal function	N	C_{max} (μg/mL)	t_{max}[a] (h)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (μg·h/mL)	Geometric mean ratio [90% CI][c]	
							C_{max}	$AUC_{0-\infty}$
Unchanged zilucoplan	Normal function	8	4.830 (18)	4.00 [2.0, 12.1]	175.87 (18)	821.51 (20)	0.93 [0.82, 1.05]	0.87 [0.74, 1.03]
	Severe impairment	8	4.469 (8)	6.00 [2.0, 12.0]	165.69 (21)	717.14 (17)		
RA102758	Normal function	8	0.119 (19)	71.95 [71.1, 96.0]	104.60 (22)[c]	25.20 (40)[c]	0.88 [0.72, 1.08]	0.91 [0.60, 1.36]
	Severe impairment	8	0.105 (27)	107.60 [47.7, 120]	116.59 (19)[d]	22.86 (30)[d]		
RA103488	Normal function	8	0.179 (21)	118.75 [71.9, 120]	296.67 (19)	100.57 (31)	1.47 [1.25, 1.73]	1.38 [0.99, 1.94]
	Severe impairment	8	0.264 (16)	119.85 [95.7, 120]	242.29 (24)[e]	139.00 (42)[e]		

Geometric mean (coefficient of variation, %)
a) Median [Min, Max]; b) Severe renal impairment to normal renal function ratio for C_{max} or $AUC_{0-\infty}$; c) N = 7; d) N = 4; e) N = 6

6.2.5 Pharmacodynamics

6.2.5.1 Effects on QT/QTc interval (CTD 5.3.4.1.1, Study UP0093)

A double-blind study was conducted to investigate the effects of zilucoplan on QT/QTc intervals in healthy non-Japanese adults (N = 64 for pharmacodynamic evaluation [32 subjects each in the zilucoplan and control groups]). Subjects were to receive zilucoplan 0.6 mg/kg subcutaneously once daily for 7 days, or a single oral dose of moxifloxacin 400 mg.

Table 26 shows the plasma pharmacokinetic parameters of unchanged zilucoplan on Day 1 and Day 7 after multiple doses of zilucoplan 0.6 mg/kg. The difference in the change from time-matched baseline in QT interval corrected with Fridericia's formula (QTcF) compared to placebo (ΔΔQTcF) was evaluated. Table 27 shows the least squares mean and its 90% confidence interval for ΔΔQTcF. The upper bound of the 90% confidence interval was <10 msec at all timepoints in the zilucoplan group.

One subject had an absolute value of the QTcF increasing to >450 msec after receiving zilucoplan 0.6 mg/kg. No subjects had absolute QTcF values >480 msec or a change from baseline of >30 msec.

19) Healthy adults matched with subjects with severe renal impairment in terms of age-, sex-, and BMI.
20) Creatinine clearance estimated by Cockroft-Gault formula.

Table 26. Plasma pharmacokinetic parameters of unchanged zilucoplan in healthy non-Japanese adults after multiple subcutaneous doses of zilucoplan 0.6 mg/kg

Timepoint	N	C_{max} (μg/mL)	t_{max} [a)] (h)	AUC_{tau} (μg·h/mL)
Day 1	32	8.37 (11.52)	4.01 [2.00, 8.05]	149.00 (9.32)
Day 7	30	23.94 (11.37)	4.00 [1.97, 10.1]	459.10 (11.20)

Geometric mean (coefficient of variation, %)
a) Median [Min, Max]

Table 27. The ΔΔQTcF values after administration of zilucoplan or moxifloxacin to healthy non-Japanese adults

	Drug	Time point	Hours post-dose									
			0.5 hours	1 hour	2 hours	3 hours	4 hours	6 hours	8 hours	10 hours	12 hours	24 hours
ΔΔQTcF interval	Zilucoplan (0.6 mg/kg)	Day 1	-4.2 [-7.20, -1.14]	1.2 [-1.30, 3.65]	1.2 [-1.58, 4.00]	1.4 [-1.16, 4.03]	3.8 [1.42, 6.16]	-0.4 [-3.55, 2.66]	0.8 [-2.29, 3.86]	1.4 [-1.31, 4.05]	3.4 [0.39, 6.42]	1.9 [-1.24, 5.05]
		Day 7	-2.8 [-6.22, 0.53]	2.8 [-0.43, 5.94]	2.3 [-1.21, 5.82]	3.2 [-0.18, 6.59]	3.9 [0.40, 7.42]	1.4 [-3.14, 5.84]	1.1 [-2.43, 4.70]	1.1 [-2.72, 4.90]	6.1 [2.91, 9.29]	1.8 [-1.57, 5.16]
	Moxifloxacin (400 mg)	Day 1	-4.0 [-6.90, -1.14]	3.4 [0.22, 6.61]	10.1 [7.22, 12.97]	8.6 [5.67, 11.46]	8.9 [5.67, 12.14]	5.9 [1.69, 10.16]	8.8 [6.50, 11.12]	7.5 [4.03, 10.88]	8.0 [4.70, 11.36]	3.5 [0.78, 6.16]

Least squares mean (msec) [90% CI]

6.2.6 PPK analysis (reference data, CTD 5.3.3.5.1, CL0508 analysis)

Population pharmacokinetic analyses (NONMEM version 7.5) were performed using plasma pharmacokinetic data for unchanged zilucoplan (2174 plasma concentration data from 200 subjects) obtained from the following studies: 4 phase I studies in healthy adults, including Japanese subjects (Studies UP0112, UP0113, UP0114, and UP0093); a phase II study in non-Japanese patients with gMG (Study MG0009); and a phase III study in patients with gMG, including Japanese patients (Study MG0010). The pharmacokinetics of unchanged zilucoplan was described by a 2-compartment model with first-order absorption followed by a target-mediated exposure enhancement (TMEE) model. The base model was developed by adding body weight as a covariate for clearance (CL and Q), volume of distribution (Vc and Vp), and absorption rate constant (ka), and potential covariates[21)] for pharmacokinetic parameters of unchanged zilucoplan were explored. No covariates, other than body weight, were added to the final model as statistically significant covariates.

Table 28 shows the a posteriori estimates of pharmacokinetic parameters in subjects in Study MG0010 based on the PPK model.

Table 28. Estimated pharmacokinetic parameters in Study MG0010 based on the PPK model

	N	C_{max} (μg/mL)	$AUC_{0\text{-}24h}$ (μg·h/mL)	C_{trough} (μg/mL)
≥43 kg and <56 kg	13	13.94 [11.01, 15.89]	295.15 [231.96, 341.52]	10.83 [8.31, 12.82]
≥56 kg and <77 kg	78	14.95 [11.36, 20.86]	314.42 [230.54, 465.64]	11.47 [8.02, 17.85]
≥77 kg and ≤150 kg	106	16.02 [10.32, 22.01]	343.04 [223.30, 485.37]	12.46 [7.90 18.51]
>150 kg	2	13.31, 13.42[a)]	290.89, 292.31[a)]	10.65, 10.79[a)]

Median [range]; a) Individual values

6.R Outline of the review conducted by PMDA

6.R.1 Ethnic differences in pharmacokinetics

The applicant's explanation:

There were no clear differences in the pharmacokinetics of unchanged zilucoplan and its metabolites between the Japanese and non-Japanese populations after administration of zilucoplan, based on the following grounds:

- In the phase I study (Study UP0113) in healthy Japanese and non-Japanese adults, the pharmacokinetic parameters of unchanged zilucoplan and its metabolites (RA102758 and RA103488) following

21) The following were investigated as potential covariates for CL and R_{max}: body weight, age, sex, race, and healthy adult vs. patient with gMG.

administration of single subcutaneous dose of zilucoplan 0.1 or 0.3 mg/kg (Table 17) or multiple subcutaneous doses of 0.3 mg/kg (Table 18) in Japanese subjects did not differ markedly from those in non-Japanese subjects.

- Table 29 shows the trough concentrations of unchanged zilucoplan in plasma following once-daily subcutaneous administration of zilucoplan at a dose (16.6, 23.0, or 32.4 mg) according to body weight (corresponding to 0.3 mg/kg) in the global phase III study (Study MG0010) conducted in Japanese and non-Japanese patients with gMG. The trough concentrations in Japanese subjects did not differ markedly from those in non-Japanese subjects.

Table 29. Trough concentrations of unchanged zilucoplan in plasma following once-daily subcutaneous administration of zilucoplan at a dose according to body weight (corresponding to 0.3 mg/kg) to Japanese and non-Japanese subjects

	Japanese			Non-Japanese		
Timepoint	≥43 kg and <56 kg (N = 1)	≥56 kg and <77 kg (N = 4)	≥77 kg and <150 kg (N = 2)	≥43 kg and <56 kg (N = 4)	≥56 kg and <77 kg (N = 15)	≥77 kg and <150 kg (N = 57)
Week 1	11.05	11.03 (14.9) 10.57 [9.70, 13.65]	10.90, 13.31	8.57 (16.0) 8.29 [7.33, 10.69]	10.63 (20.8)[b)] 10.33 [8.01, 15.51]	11.90 (20.8)[e)] 11.94 [6.17, 17.79]
Week 2	12.22	12.180 (15.4) 11.57 [10.82, 15.22]	14.41, 16.83	9.43 (14.8) 9.17 [8.35, 11.35]	11.58 (18.4)[b)] 11.51 [7.20, 15.74]	12.86 (22.3) 12.74 [8.21, 20.13]
Week 4	12.23	13.26 (18.8) 12.30 [11.75, 17.44]	12.49, 17.81	10.06 (16.9) 9.76 [8.52, 12.63]	12.50 (18.8)[c)] 12.85 [8.32, 18.10]	12.75 (41.8)[e)] 13.34 [1.41, 20.75]
Week 8	12.68	12.75 (20.9) 11.73 [11.15, 17.27]	12.38, 16.51	8.50 (12.1)[a)] 8.77 [7.44, 9.41]	11.50 (28.3)[d)] 12.17 [5.74, 16.84]	12.82 (23.2)[f)] 13.19 [8.05, 20.54]
Week 12	12.15	13.56 (19.2) 12.55 [11.95, 17.99]	12.67, 17.19	1.51 (764.6) 4.10 [0.15, 8.79]	11.80 (19.8)[b)] 12.12 [7.66, 15.89]	11.46 (101.6)[g)] 12.55 [0.034, 20.11]

Upper row, Geometric mean, μg/mL (coefficient of variation, %); Lower row, Median [range]
a) N = 3; b) N = 14; c) N = 13; d) N = 12; e) N = 56; f) N = 55; g) N = 53

- Table 30 shows the estimated pharmacokinetic parameters of unchanged zilucoplan at steady state based on simulations with the PPK model [see Section 6.2.6] in Japanese and non-Japanese subjects following multiple subcutaneous administration of zilucoplan at a dose according to body weight (corresponding to 0.3 mg/kg) for 4 weeks. The results show no clear differences between the Japanese and non-Japanese populations.

Table 30. Estimated pharmacokinetic parameters of unchanged zilucoplan at steady state following multiple subcutaneous administration of zilucoplan at a dose (corresponding to 0.3 mg/kg) for 4 weeks

Japanese (N = 21)		Non-Japanese (N = 134)	
$C_{max,ss}$ (μg/mL)	$AUC_{0\text{-}24,ss}$ (μg·h/mL)	$C_{max,ss}$ (μg/mL)	$AUC_{0\text{-}24,ss}$ (μg·h/mL)
16.0 (11.8) 15.5 [13.6, 20.4]	337 (13.3) 324 [289, 438]	15.1 (17.2) 15.0 [10.3, 22.0]	323 (17.8) 316 [223, 485]

Upper row, Geometric mean (coefficient of variation, %); Lower row, Median [range]

PMDA's view:

The submitted data indicate that there were no ethnic differences in the pharmacokinetics of unchanged zilucoplan and its metabolites in subjects receiving zilucoplan.

6.R.2 Appropriateness of dosage regimen from a clinical pharmacology perspective

The applicant's explanation from a clinical pharmacology perspective concerning the rationale for the regimen of zilucoplan employed in the global phase III study (Study MG0010) and the appropriateness of the proposed dosage regimen of zilucoplan:

- In the foreign phase I study (Study UP0112), the mean percent change from baseline in the inhibition of sheep red blood cell (sRBC) hemolysis following a single dose of zilucoplan 0.4 mg/kg was 97% at 24 hours post-dose and decreased to 88% at 48 hours post-dose. Therefore, in Study MG0009, zilucoplan was to be injected once daily subcutaneously into the areas of the abdomen, thigh, or upper arm.
- In Study UP0112, the protocol specified dose levels per kg of body weight (0.05 to 0.4 mg/kg). In Study MG0009, however, the body weight band-based dosage regimen was selected for ease of administration. In a foreign phase II study in patients with paroxysmal nocturnal hemoglobinuria, the administration of subcutaneous zilucoplan 0.1 or 0.3 mg/kg once daily inhibited sRBC hemolysis to some extent, and the dose of 0.42 mg/kg was the highest dosage demonstrated to be safe. Based on the results and other factors, the body weight band-based dosage regimen was employed in Study MG0009 (Table 31). The dose according to the dosage regimen was in the range of ≥0.1 mg/kg and ≤0.14 mg/kg for all body weight bands in the 0.1 mg/kg group and in the range of ≥0.3 mg/kg and ≤0.42 mg/kg for all body weight bands in the 0.3 mg/kg group.

Table 31. Treatment groups and dosage regimens (Study MG0009)

Treatment	Body weight band	Dose of zilucoplan (mg)	(Reference information) Range of actual dose per kg of body weight (mg/kg/day)
Zilucoplan 0.1 mg/kg	≥43 kg and <61 kg	6.0	≥0.10 and ≤0.14
	≥61 kg and <88 kg	8.8	≥0.10 and ≤0.14
	≥88 kg and <109 kg[a)]	12.4	≥0.11 and ≤0.14
Zilucoplan 0.3 mg/kg	≥43 kg and <56 kg	16.6	≥0.30 and ≤0.39
	≥56 kg and <77 kg	23.0	≥0.30 and ≤0.41
	≥77 kg and <109 kg[a)]	32.4	≥0.30 and ≤0.42

a) The dose for subjects weighing ≥109 kg was determined by the principal investigator on an individual basis.

- Based on the results of Study MG0009 [see Section 7.2.1], the following dosage regimen was selected in the global phase III study in patients with gMG (Study MG0010): subjects were to receive zilucoplan by subcutaneous injection into the areas of the abdomen, thigh, or upper arm once daily at a dose based on the body weight band corresponding to that used in the 0.3 mg/kg group in Study MG0009 [see Sections 7.3.1 and 7.3.2]. Since some subjects enrolled in Study MG0009 weighed ≥109 kg, taking into account safety data for subjects in this body weight group as well as the results of simulation with the PPK model, 150 kg was selected as the upper limit of the heaviest weight band for the dosage regimen used in Study MG0010. The dosage for patients weighing <43 kg and those weighing >150 kg was to be determined by the principal investigator on an individual basis only after taking body weight, medical history, comorbidities, and laboratory data into account. The results of Study MG0010 show that the range of individual trough concentrations of unchanged zilucoplan in plasma following once-daily subcutaneous administration of zilucoplan at a dose based on the body weight band overlaps with the range of trough concentrations for other body weight bands (Table 32).

Table 32. Trough concentrations of unchanged zilucoplan in plasma at each timepoint by body weight

Timepoint	≥43 kg and <56 kg (N = 5)	≥56 kg and <77 kg (N = 19)	≥77 kg and ≤150 kg (N = 58)
Week 1	9.01 (18.0) 8.34 [7.33, 11.05]	10.99 (21.9) 10.49 [8.01, 17.42]	11.82 (20.0)[a)] 11.88 [6.17, 17.79]
Week 2	9.93 (17.3) 9.93 [8.35, 12.22]	11.92 (18.8) 11.55 [7.20, 16.54]	12.89 (22.2) 12.89 [8.21, 20.13]
Week 4	10.46 (17.1) 10.11 [8.52, 12.63]	13.03 (21.4)[b)] 12.82 [8.32, 20.75]	13.22 (26.8)[c)] 13.34 [3.72, 19.87]
Week 8	9.39 (22.6)[d)] 9.09 [7.44, 12.68]	12.13 (28.0)[e)] 12.27 [5.74, 18.61]	12.78 (22.7)[c)] 13.10 [8.05, 20.54]
Week 12	9.36 (24.0)[f)] 8.79 [7.67, 12.15]	12.50 (22.7) 12.36 [7.66, 20.11]	12.77 (21.4)[g)] 12.67 [7.08, 17.88]

Upper row, Geometric mean, μg/mL (coefficient of variation, %); Lower row, Median [range]
a) N = 57; b) N = 18; c) N = 56; d) N = 4; e) N = 17; f) N = 3; g) N = 53

Based on the above, the dosage regimen specified in the protocol of Study MG0010 was selected as the proposed dosage regimen. In addition, given that results from Studies MG0010 and UP0115 showed no differences in pharmacokinetics regardless of injection sites (abdomen, thigh, or upper arm) [see Section 6.1], the applicant decided that zilucoplan should be injected into the areas of the abdomen, thigh, or upper arm.

The "Precautions Concerning Dosage and Administration" section in the proposed package insert included a cautionary statement to the effect that physicians are advised to consider administering zilucoplan 16.6 mg to patients weighing <43 kg and zilucoplan 32.4 mg to those weighing >150 kg. PMDA asked the applicant to explain, from a clinical pharmacology perspective, the appropriateness of the dosage regimens for patients weighing <43 kg and for those weighing >150 kg:

The applicant's explanation:
Studies MG0009 and MG0011 included 1 patient weighing <43 kg (41.4 kg) and 5 patients weighing >150 kg (155-171.1 kg). The former patient received zilucoplan 16.6 mg and the latter 5 patients received zilucoplan 32.4 mg. Table 33 shows the plasma trough concentrations of unchanged zilucoplan in these patients, which generally fell within the range of plasma trough concentrations of unchanged zilucoplan in patients weighing ≥43 kg and ≤150 kg.

Table 33. Plasma trough concentrations of unchanged zilucoplan at each timepoint in Study MG0011 by body weight band

	Zilucoplan 0.3 mg/kg / zilucoplan 0.3 mg/kg			Placebo / zilucoplan 0.3 mg/kg		
Timepoint[a)]	<43 kg	≥43 kg and ≤150 kg	>150 kg	<43 kg	≥43 kg and ≤150 kg	>150 kg
Week 1	—	7.19, 21.50 (63)	10.53, 11.13 (2)	14.52 (1)	BLQ, 21.42 (57)	5.84, 10.09 (2)
Week 24	—	6.07, 38.71 (64)	11.28, 11.65 (2)	18.70 (1)	1.93, 23.38 (49)	7.89, 11.44 (2)
Week 48	—	7.21, 24.06 (36)	8.32 (1)	17.91 (1)	8.29, 23.71 (28)	7.92 (1)

Min, Max, or individual value, μg/mL (N)
a) Week number in Study MG0011

- The plasma zilucoplan concentrations after administration of zilucoplan 16.6 mg to patients weighing <43 kg and zilucoplan 32.4 mg to patients weighing >150 kg were simulated based on the PPK model [see Section 6.2.6]. The estimated medians (with 90% prediction interval) for the parameters at steady state were 16.34 [13.03, 20.61] μg/mL (C_{max}), 340.0 [260.5, 436.7] μg·h/mL (AUC_{0-24}), and 12.45 [9.21, 16.35] μg/mL (C_{trough}) for patients weighing <43 kg; and 10.75 [8.64, 13.93] μg/mL (C_{max}), 244.2 [198.2, 318.3] μg·h/mL (AUC_{0-24}), and 9.30 [7.51, 12.35] μg/mL (C_{trough}) for patients weighing >150 kg. The estimated

exposures after administration of zilucoplan 16.6 mg to patients weighing <43 kg were distributed within the range of individual exposure values of subjects weighing ≥43 kg and ≤150 kg in Study MG0010 (Table 28). The estimated exposures after administration of zilucoplan 32.4 mg to patients weighing >150 kg tend to be lower than the exposures in subjects weighing ≥43 kg and ≤150 kg in Study MG0010; however, the range of the estimated exposures generally overlapped the range of the exposure data from the study. A PPK/population pharmacodynamic (PD) analysis (CL0544 analysis) was performed to investigate the relationship between plasma zilucoplan concentrations and sRBC hemolysis inhibition using data from Studies MG0009 and MG0010. The EC_{95} for the inhibition of sRBC hemolysis was estimated to be 4.45 μg/mL; therefore, the plasma trough concentration (C_{trough}) in patients weighing >150 kg after administration of zilucoplan 32.4 mg is inferred to exceed the EC_{95}.

Based on the above, it is possible to choose the same dosage for patients weighing <43 kg as that for patients weighing ≥43 kg and <56 kg, and the same dosage for patients weighing >150 kg as that for patients weighing ≥77 kg and ≤150 kg.

PMDA's view:
The protocol of Study MG0010 specified that subjects should receive zilucoplan at a dose based on the body weight band (Table 44) once daily by subcutaneous injection into the areas of the abdomen, thigh, or upper arm, and this protocol is appropriate. The results of Studies MG0010 and MG0011 show that the ranges of distribution of individual exposures (C_{max} and AUC) in subjects receiving zilucoplan at a dose based on the body weight band (Table 44) generally overlapped between different body weight bands. From a clinical pharmacology perspective, selecting the same dosage regimen as that used in Study MG0010 for patients weighing ≥43 kg or those weighing ≤150 kg is appropriate.

Although the experience with the use of zilucoplan in patients weighing <43 kg or those weighing >150 kg is limited, given the results of simulation with the PPK model as well as other data, the exposures in these patient populations are unlikely to deviate markedly from the range of exposures in subjects treated with zilucoplan 0.3 mg/kg in Study MG0010. Therefore, from a clinical pharmacology perspective, the dosage for patients weighing <43 kg should be the same as that for patients weighing ≥43 kg and <56 kg, and the dosage for patients weighing >150 kg should be the same as that for patients weighing ≥77 kg and ≤150 kg.

6.R.3 Immunogenicity

The applicant's explanation:
The pharmacokinetics, efficacy, and safety of zilucoplan are unlikely to be affected by ADAs and anti-PEG antibodies (APAs) that developed after administration of zilucoplan based on the following grounds.

In Study MG0010, 2 subjects (2.3%) tested positive for ADAs and 8 subjects (9.3%) tested positive for APAs.

Table 34 shows plasma zilucoplan concentrations in subjects who were positive for ADAs or APAs. The results show no clear differences from the overall population.

Table 34. Plasma zilucoplan concentrations in subjects who were positive for ADAs or APAs

Timepoint	ADA positive	APA positive	Overall population
Week 1	7.33, 14.79 (2)	7.33, 17.42 (8)	6.17, 17.79 (81)
Week 2	8.35, 15.12 (2)	8.35, 17.83 (8)	7.20, 20.13 (82)
Week 4	8.52, 19.68 (2)	3.72, 20.75 (8)	3.72, 20.75 (79)
Week 8	9.41, 15.32 (2)	7.44, 18.61 (8)	5.74, 20.54 (77)
Week 12	7.67, 11.51 (2)	7.67, 20.11 (7)	7.08, 20.11 (75)

Min, Max in μg/mL (number of subjects evaluated)

The efficacy data showed that the Myasthenia Gravis Activities of Daily Living (MG-ADL) total score and its change from baseline at Week 12 for each of the 2 subjects who were ADA-positive was 10 (change from baseline = 0) and 4 (change from baseline = −11), indicating no clear difference from the overall population (Table 45). Table 35 shows the MG-ADL total scores in subjects who were APA-positive and in subjects who were APA-negative. The results showed no clear differences between subjects who were APA-positive and those who were APA-negative.

Table 35. MG-ADL total score in subjects who were APA-positive or negative

	Baseline	Week 12
APA-positive	11.3 ± 2.1 (N = 8) 11.0 (8, 15)	8.6 ± 5.1 (N = 8) 9.5 (1, 14)
APA-negative	10.2 ± 2.5 (N = 78) 10.0 (6, 16)	5.2 ± 3.8 (N = 76) 4.0 (0, 14)

Upper row, Mean ± standard deviation (number of subjects evaluated); Lower row, Median (Min, Max)

Safety data were analyzed. Adverse events occurring in the 2 subjects who were ADA-positive were musculoskeletal pain (mild), headache (mild), and myasthenia gravis (moderate) in 1 subject; and arrhythmia (moderate) in the other subject. These adverse events in the 2 ADA-positive subjects raised no significant concerns compared to those in ADA-negative subjects. Table 36 shows the summary of adverse events in subjects who were APA-positive and those who were APA-negative. The results indicated no differences between subjects who were APA-positive and those who were APA-negative.

Table 36. Summary of adverse events in subjects who were APA-positive and those who APA-negative

	APA-positive (N = 8)	APA-negative (N = 78)
All adverse events	5 (62.5)	61 (78.2)
Serious adverse events	3 (37.5)	8 (10.3)
Adverse events leading to study drug discontinuation	1 (12.5)	3 (3.8)
Adverse events which were considered related to the study drug	3 (37.5)	25 (32.1)

n (%)

PMDA's view:

While the number of subjects who were ADA-positive or APA-positive after treatment with zilucoplan was small, the applicant's explanation ("the pharmacokinetics, efficacy, and safety of zilucoplan are unlikely to be affected by ADAs and APAs that developed after administration of zilucoplan") is reasonable. The development of ADAs or APAs is less likely to cause clinically relevant problems.

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

The applicant submitted efficacy and safety evaluation data, in the form of results data from clinical studies as summarized in Table 37.

Table 37. List of clinical studies on efficacy and safety

Data	Location	Study ID CTD	Phase	Study population	Number of subjects enrolled	Summary of dosage regimen	Main endpoint
Evaluation	Foreign	UP0113 5.3.3.1.2	I	Healthy Japanese and non-Japanese adults	36	Single-dose cohort: single subcutaneous dose of placebo or zilucoplan 0.1 or 0.3 mg/kg Multiple-dose cohort: multiple subcutaneous doses of placebo or zilucoplan 0.3 mg/kg once daily (14 days)	Safety Pharmacokinetics
	Foreign	MG0009 5.3.5.1.1	II	Adult patients with gMG	45	Subcutaneous dose of zilucoplan 0.1 mg/kg/day, zilucoplan 0.3 mg/kg/day, or placebo once daily	Efficacy Safety
	Global	MG0010 5.3.5.1.2	III	Adult patients with gMG	174	Subcutaneous dose of placebo or zilucoplan 0.3 mg/kg/day once daily	Efficacy Safety
	Global	MG0011 5.3.5.2.1 and 5.3.5.2.2	III	Adult patients with gMG	200	Subcutaneous dose of zilucoplan 0.3 mg/kg/day once daily	Efficacy Safety

7.1 Phase I study

7.1.1 Foreign phase I study (CTD 5.3.3.1.2, Study UP0113 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A clinical study consisting of a single-dose cohort and a multiple-dose cohort was conducted outside Japan to evaluate the safety and pharmacokinetics of zilucoplan after a single dose of or multiple doses of zilucoplan in healthy Japanese and non-Japanese adults (target sample size, 36 subjects) [for pharmacokinetics, see Section 6.2.2.1].

Subjects in the single-dose cohort were to receive a single subcutaneous dose of placebo or zilucoplan 0.1 or 0.3 mg/kg, and those in the multiple-dose cohort were to receive multiple subcutaneous doses of placebo or zilucoplan 0.3 mg/kg for 14 days. The single-dose cohort consisted of the zilucoplan 0.1 mg/kg cohort [Cohort 1] and zilucoplan 0.3 mg/kg cohort [Cohort 2], each containing 5 Japanese and 5 non-Japanese subjects. Of the 5 subjects in each cohort, 1 was randomly assigned to the placebo group and 4 to the zilucoplan group. The multiple-dose cohort had 8 Japanese and 8 non-Japanese subjects. Of the 8 subjects, 2 were randomly assigned to the placebo group and 6 to the zilucoplan group.

All the 36 randomized subjects received the study drug (8 subjects in the placebo group and 28 subjects in the zilucoplan group) and were included in the safety analysis set. No subjects discontinued study treatment.

According to safety analysis for the single-dose cohort, the incidence of adverse events was 25.0% (1 of 4 subjects) in the placebo group (Cohorts 1 and 2), 12.5% (1 of 8 subjects) in the zilucoplan 0.1 mg/kg group (Cohort 1), and 12.5% (1 of 8 subjects) in the zilucoplan 0.3 mg/kg group (Cohort 2). According to safety analysis for the multiple-dose cohort, the incidence of adverse events was 25.0% (1 of 4 subjects) in the placebo group and 16.7% (2 of 12 subjects) in the zilucoplan 0.3 mg/kg group. There were no serious adverse events including death or adverse events leading to treatment discontinuation in either cohort.

In the single-dose cohort, the following adverse events were reported in the placebo group, zilucoplan 0.1 mg/kg group, and zilucoplan 0.3 mg/kg group: papule (0 subjects, 0 subjects, and 1 subject, respectively), injection site pain (0 subjects, 1 subject, and 0 subjects, respectively), upper respiratory tract infection (1 subject, 0 subjects, and 0 subjects, respectively), neck pain (1 subject, 0 subjects, and 0 subjects, respectively), and headache (1 subject, 0 subjects, and 0 subjects, respectively). In the multiple-dose cohort, the following adverse events were reported in the placebo group and zilucoplan 0.3 mg/kg group: photophobia (0 subjects and 1 subject, respectively), abdominal pain (0 subjects and 1 subject, respectively), constipation (0 subjects and 1 subject, respectively), injection site pain (0 subjects and 1 subject, respectively), musculoskeletal pain (0 subjects and 1 subject, respectively), and headache (1 subject and 0 subjects, respectively).

7.2 Phase II study

7.2.1 Foreign phase II study (CTD 5.3.5.1.1, Study MG0009 [November 2017 to November 2020])

A randomized, double-blind, placebo-controlled, parallel-group study consisting of the main portion (12 weeks) and extension portion (up to 116 weeks after the start of treatment) was conducted in 2 countries (the US and Canada) to evaluate the efficacy, safety, and other aspects of zilucoplan in patients with gMG who were anti-AChR antibody positive (target sample size, 36 subjects; 12 per group[22)]).

The key inclusion criteria were diagnosis of gMG at screening (Myasthenia Gravis Foundation of America [MGFA] Class II to IVa); anti-AChR antibody-positive status; and Quantitative Myasthenia Gravis (QMG) score of ≥12 points with ≥4 items scored ≥2 points at screening and baseline, off acetylcholinesterase inhibitor therapy for at least 10 hours.

(1) Main portion

Subjects were to receive placebo or zilucoplan subcutaneously once daily for 12 weeks. The dose of zilucoplan was determined based on Table 38.

Table 38. Treatment groups and dosage regimens (Study MG0009)

Treatment	Body weight band	Dose of zilucoplan (mg)	(Reference information) Range of actual dose per kg of body weight (mg/kg/day)
Zilucoplan 0.1 mg/kg	≥43 kg and <61 kg	6.0	≥0.10 and ≤0.14
	≥61 kg and <88 kg	8.8	≥0.10 and ≤0.14
	≥88 kg and <109 kg[a)]	12.4	≥0.11 and ≤0.14
Zilucoplan 0.3 mg/kg	≥43 kg and <56 kg	16.6	≥0.30 and ≤0.39
	≥56 kg and <77 kg	23.0	≥0.30 and ≤0.41
	≥77 kg and <109 kg[a)]	32.4	≥0.30 and ≤0.42

a) The dose for subjects weighing ≥109 kg was determined by the principal investigator on an individual basis.

Randomization was stratified based on the QMG total score at screening (≤17 or ≥18 points), and subjects were randomized to placebo, zilucoplan 0.1 mg/kg, or 0.3 mg/kg.

22) For the change from baseline in QMG total score at Week 12, the primary endpoint, assuming a difference of 4.5 points between zilucoplan and placebo with a standard deviation of 5.0 points, a target size of 12 subjects per group was selected to detect the difference at approximately 81% power with a one-sided significant level of 10%.

Of the 45 randomized subjects (15 subjects each per group), 1 subject who did not receive the study drug (zilucoplan 0.3 mg/kg) was excluded. The remaining 44 subjects (15 subjects [placebo], 15 subjects [zilucoplan 0.1 mg/kg], and 14 subjects [zilucoplan 0.3 mg/kg]) were included in the safety analysis set and modified Intention-to-Treat (mITT) population. The mITT population was the population used for efficacy analyses. In the main portion of the study, 2 subjects (0 subjects [placebo], 0 subjects [zilucoplan 0.1 mg/kg], and 2 subjects [zilucoplan 0.3 mg/kg]) discontinued study treatment due to "lost to follow-up" and "withdrawal of consent" (1 subject each).

Table 39 shows the change from baseline in QMG total score[23)] at Week 12, the primary endpoint. The results show statistically significant differences between zilucoplan 0.1 mg/kg and placebo and between zilucoplan 0.3 mg/kg and placebo.

Table 39. Change from baseline in QMG total score at Week 12 (mITT population, LOCF)

	N	Baseline[a)]	Week 12[a)]	Change from baseline[b), c)]	Difference from placebo in change from baseline[c), d)] [80% CI]	*P*-value[c), e)]
Placebo	15	18.7 ± 4.0 17.0 (14, 30)	15.5 ± 5.5 14.0 (8, 27)	-3.2 ± 1.2		
Zilucoplan 0.1 mg/kg	15	18.7 ± 4.0 18.0 (13, 29)	13.3 ± 5.6 12.0 (7, 25)	-5.5 ± 1.2	-2.3 [-4.5, -0.1]	0.0941
Zilucoplan 0.3 mg/kg	14	19.1 ± 5.1 18.5 (12, 33)	12.9 ± 3.8 13.0 (3, 19)	-6.0 ± 1.2	-2.8 [-5.1, -0.6]	0.0538

a) Upper row, Mean ± standard deviation; Lower row, Median (Min, Max)
b) Least squares mean ± standard error
c) Calculated based on an ANCOVA model with treatment as a fixed effect and baseline QMG total score as a covariate
d) Difference from placebo in mean change from baseline
e) Pairwise comparison of each of treatment groups with placebo, at a one-side significance level of 0.10
Zilucoplan 0.3 mg/kg vs. placebo is for the primary analysis and zilucoplan 0.1 mg/kg vs. placebo is for the secondary analysis.

Table 40 shows the incidence of any adverse event and the incidence of adverse events occurring in ≥2 subjects in any group.

Table 40. Incidence of any adverse event and incidence of adverse events occurring in ≥2 subjects in any group (safety analysis set)

	Placebo (N = 15)	Zilucoplan 0.1 mg/kg (N = 15)	Zilucoplan 0.3 mg/kg (N = 14)
Any adverse event	14 (93.3)	15 (100)	12 (85.7)
Adverse events occurring in ≥2 subjects in any group			
Headache	4 (26.7)	6 (40.0)	3 (21.4)
Dermatitis contact	1 (6.7)	1 (6.7)	2 (14.3)
Amylase increased	1 (6.7)	0	2 (14.3)
Squamous cell carcinoma	0	0	2 (14.3)
Myasthenia gravis	3 (20.0)	2 (13.3)	1 (7.1)
Fatigue	1 (6.7)	2 (13.3)	1 (7.1)
Lipase increased	2 (13.3)	0	1 (7.1)
Injection site scab	0	3 (20.0)	0
Injection site bruising	2 (13.3)	2 (13.3)	0
Nausea	0	2 (13.3)	0
Dizziness	4 (26.7)	1 (6.7)	0
Pruritus	2 (13.3)	1 (6.7)	0
Joint swelling	2 (13.3)	0	0
Dyspnoea	2 (13.3)	0	0

n (%)

23) A scale system to test a total of 13 items (double vision, ptosis, facial muscles, swallowing 4 oz of water, speech after counting aloud from 1 to 50, right and left hand grip, arms outstretched, legs outstretched, head lifted, and forced vital capacity) assessed by physicians for the severity of the following: ocular/facial muscles, bulbar symptoms, gross motor/axial muscles, and respiratory muscles. All items are scored on a 4-point scale from 0 (normal) to 3 (severe), and assessed by physicians.

There were no reports of deaths. Table 41 shows serious adverse events other than death. A causal relationship to the study drug was ruled out for all events. An adverse event (myasthenia gravis) led to treatment discontinuation in 6.7% (1 of 15) of subjects in the placebo group.

Table 41. Serious adverse events other than death (safety analysis set)

Placebo	Myasthenia gravis (3 subjects)
Zilucoplan 0.1 mg/kg	None
Zilucoplan 0.3 mg/kg	Abdominal abscess/diverticulitis, systemic inflammatory response syndrome, blood culture positive, cellulitis, and musculoskeletal chest pain (1 subject each)

(2) Extension portion

Subjects were to receive once-daily subcutaneous doses of zilucoplan according to Table 38.

Subjects who had been assigned to placebo during the main portion of the study were randomized in a blinded manner in a ratio of 1:1 to receive zilucoplan 0.1 mg/kg or 0.3 mg/kg. Subjects who had been assigned to zilucoplan during the main portion of the study continued to receive the same dose in a blinded manner. Based on the analysis of the main portion, the protocol was amended during the extension portion. Consequently, subjects in the zilucoplan 0.1 mg/kg group were switched to receive zilucoplan 0.3 mg/kg.

Forty-two subjects who had completed the main portion of the study entered the extension portion and were included in the safety analysis set. Treatment discontinuation occurred in 5 subjects who entered the extension portion (2 subjects in the 0.1 mg/kg group and 3 subjects in the 0.3 mg/kg group). Treatment was discontinued in 3 subjects due to “death” (1 subject in the 0.1 mg/kg group and 2 subjects in the 0.3 mg/kg group) and 2 subjects due to “withdrawal of consent” (1 subject each in the 0.1 mg/kg and 0.3 mg/kg groups). The median duration of study treatment from the first dose was 388.5 days (range, 104-476 days) in the zilucoplan 0.1 mg/kg group (before dose switch), 253.0 days (range, 35-526 days) in the zilucoplan 0.1 mg/kg group (after dose switch), and 609 days (range, 57-851 days) in the zilucoplan 0.3 mg/kg group.

Table 42 shows the incidence of any adverse event and the incidence of adverse events occurring in ≥2 subjects in either group.

Table 42. Incidence of any adverse event and incidence of adverse events occurring in ≥2 subjects in either group (safety analysis set)

	Zilucoplan 0.1 mg/kg (N = 22)		Zilucoplan 0.3 mg/kg (N = 20)
	Before switch to zilucoplan 0.3 mg/kg (N = 22)	After switch to zilucoplan 0.3 mg/kg (N = 17)	
Any adverse event	22 (100)	17 (100)	20 (100)
Adverse events occurring in ≥2 subjects in either group			
Nasopharyngitis	6 (27.3)	5 (29.4)	8 (40.0)
Nausea	3 (13.6)	1 (5.9)	5 (25.0)
Cough	3 (13.6)	1 (5.9)	5 (25.0)
Upper respiratory tract infection	3 (13.6)	2 (11.8)	4 (20.0)
Myalgia	0	1 (5.9)	4 (20.0)
Myasthenia gravis	4 (18.2)	0	4 (20.0)
Back pain	2 (9.1)	0	4 (20.0)
Diarrhoea	1 (4.5)	0	4 (20.0)
Muscle spasms	1 (4.5)	0	4 (20.0)
Headache	6 (27.3)	3 (17.6)	3 (15.0)
Dizziness	3 (13.6)	3 (17.6)	3 (15.0)
Vomiting	2 (9.1)	2 (11.8)	3 (15.0)
Arthralgia	2 (9.1)	1 (5.9)	3 (15.0)
Injection site bruising	5 (22.7)	0	3 (15.0)
Sinusitis	2 (9.1)	0	3 (15.0)
Pneumonia	2 (9.1)	1 (5.9)	2 (10.0)
Nephrolithiasis	2 (9.1)	1 (5.9)	2 (10.0)
Oedema peripheral	1 (4.5)	1 (5.9)	2 (10.0)
Pyrexia	1 (4.5)	1 (5.9)	2 (10.0)
Fatigue	0	1 (5.9)	2 (10.0)
Cataract	0	1 (5.9)	2 (10.0)
Migraine	2 (9.1)	0	2 (10.0)
Hypoaesthesia	2 (9.1)	0	2 (10.0)
Abdominal pain upper	1 (4.5)	0	2 (10.0)
Paraesthesia	1 (4.5)	0	2 (10.0)
Rash	1 (4.5)	0	2 (10.0)
Anaemia	0	0	2 (10.0)
Abdominal distension	0	0	2 (10.0)
Dysphagia	0	0	2 (10.0)
Cholecystitis	0	0	2 (10.0)
Pancreas infection	0	0	2 (10.0)
Post procedural complication	0	0	2 (10.0)
Bursitis	0	0	2 (10.0)
Muscle twitching	0	0	2 (10.0)
Depression	0	0	2 (10.0)
Miliaria	0	0	2 (10.0)
Hypotension	0	0	2 (10.0)
Urinary tract infection	2 (9.1)	2 (11.8)	1 (5.0)
Dyspnoea	1 (4.5)	2 (11.8)	1 (5.0)
Injection site nodule	0	2 (11.8)	1 (5.0)
Pain in extremity	0	2 (11.8)	1 (5.0)
Bronchitis	2 (9.1)	0	1 (5.0)
Palpitations	2 (9.1)	0	1 (5.0)
Fall	0	2 (11.8)	0
Contusion	2 (9.1)	0	0
Lipase increased	2 (9.1)	0	0
Hypokalaemia	2 (9.1)	0	0

n (%)

Adverse events led to death in 3 subjects (COVID-19 [1 subject] in the zilucoplan 0.1 mg/kg group [after dose switch]; respiratory failure/cardiac arrest [1 subject] and pancreatic carcinoma [1 subject] in the zilucoplan 0.3 mg/kg group). All of these events were considered unrelated to the study drug. Table 43 shows the incidence of serious adverse events other than death. A causal relationship to the study drug was ruled out for all these events. Adverse events led to treatment discontinuation in 13.6% (3 of 22) of subjects in the zilucoplan 0.1 mg/kg group (dizziness in 1 subject [after dose switch], pneumonia in 1 subject, and COVID-19 in 1 subject [after dose switch]) and in 10.0% (2 of 20) of subjects in the zilucoplan 0.3 mg/kg group (pancreatic carcinoma

in 1 subject and musculoskeletal pain in 1 subject). A causal relationship to the study drug was ruled out for all these events except for dizziness in 1 subject in the zilucoplan 0.1 mg/kg group.

Table 43. Serious adverse events other than death (safety analysis set)

Zilucoplan 0.1 mg/kg	Serious adverse events reported in a total of 7 subjects: nephrolithiasis[a)]/pneumonia[a)]/sepsis[a)]/ureterolithiasis[a)]/nephrolithiasis[a)] (1 subject); pneumonia/fibrin D dimer increased/staphylococcal bacteraemia (1 subject); back pain/gastric ulcer[a)]/abdominal pain[a)] (1 subject); myasthenia gravis/pneumonia (1 subject); bradycardia[a)] (1 subject); rapidly progressive osteoarthritis (1 subject); abdominal pain (1 subject)
Zilucoplan 0.3 mg/kg	Serious adverse events reported in a total of 7 subjects: cholecystitis/post procedural complication/myocardial infarction/liver abscess/pancreatitis acute/atrial fibrillation/pancreas infection/pneumonia/intra-abdominal fluid collection/atrial flutter/myasthenia gravis (1 subject); postoperative hypertension/myasthenia gravis/spinal fracture (1 subject); pancreatic cyst/myasthenia gravis/post procedural complication/pancreas infection (1 subject); staphylococcal bacteraemia (1 subject); gastrointestinal infection (1 subject); non-cardiac chest pain/syncope (1 subject); cholecystitis (1 subject)

a) After switch to 0.3 mg/kg.

7.3 Phase III studies

7.3.1 Global phase III study (CTD 5.3.5.1.2, Study MG0010 [September 2019 to December 2021])

A randomized, double-blind, placebo-controlled, parallel-group study was conducted in 10 countries[24)] to evaluate the efficacy, safety, and other aspects of zilucoplan in patients with gMG who were anti-AChR antibody positive (target sample size, 156 subjects; 78 subjects per group[25)]).

The key inclusion criteria were diagnosis of gMG at screening (MGFA Class II to IV); anti-AChR antibody-positive status; MG-ADL total score of ≥6 points at screening and baseline; QMG total score of ≥12 points, with ≥4 items scored ≥2 points at screening and baseline, off acetylcholinesterase inhibitor therapy for at least 10 hours.

Subjects were to receive placebo or zilucoplan subcutaneously once daily for 12 weeks. The dose of zilucoplan was to be determined based on Table 44

Table 44. Treatment group and dosage regimens (Study MG0010)

Treatment	Body weight band	Dose of zilucoplan (mg)	(Reference information) Range of actual dose per kg of body weight (mg/kg/day)
Zilucoplan 0.3 mg/kg	≥43 kg and <56 kg[a)]	16.6	≥0.30 and ≤0.39
	≥56 kg and <77 kg	23.0	≥0.30 and ≤0.41
	≥77 kg and ≤150 kg[a)]	32.4	≥0.22 and ≤0.42

a) The dose for subjects weighing >150 kg or <43 kg was determined by the principal investigator on an individual basis.

Randomization was stratified based on the baseline MG-ADL total score (≤9 or ≥10), the baseline QMG total score (≤17 or ≥18), and geographical region (North America, Europe, or East Asia), and subjects were randomized in a 1:1 ratio to receive zilucoplan or placebo.

All the 174 randomized subjects (88 subjects [placebo] and 86 subjects [zilucoplan 0.3 mg/kg]) were included in the safety analysis set and the mITT population. The mITT population was the population used for efficacy

24) Japan, the US, Canada, France, Germany, Italy, Norway, Poland, Spain, and the UK

25) For the change from baseline in MG-ADL total score at Week 12, the primary endpoint, assuming a difference of 2.3 points between the zilucoplan and placebo groups with a standard deviation of 3.7 points, and 65 subjects per group, the study would provide approximately 94% power to detect the difference between the zilucoplan and placebo groups at a two-sided significance level of 0.05. A target sample size of 78 subjects per group was selected taking into account of the rates of rescue therapy use and dropout of up to 10% and 5%, respectively.

analyses. Treatment discontinuation occurred in 8 subjects (4 subjects [placebo] and 4 subjects [zilucoplan 0.3 mg/kg]). Treatment was discontinued in 3 subjects due to "withdrawal of consent" (2 subjects [placebo] and 1 subject [zilucoplan 0.3 mg/kg]) and in 2 subjects due to "death" (1 subject [placebo] and 1 subject [zilucoplan 0.3 mg/kg]), and other reasons were "adverse events" (0 subjects [placebo] and 2 subjects [zilucoplan 0.3 mg/kg]) and "investigator's decision" (1 subject [placebo] and 0 subjects [zilucoplan 0.3 mg/kg]).

Table 45 shows the change[26)] from baseline in MG-ADL total score[27)] at Week 12, the primary endpoint. The results show a statistically significant difference between the zilucoplan 0.3 mg/kg group and placebo group.

Table 45. Change from baseline in MG-ADL total score at Week 12 (mITT population)

	Baseline[a)]	Week 12[a)]	Change from baseline[b), c)]	Difference between groups in change from baseline[c), d)] [95% CI]	*P*-value[c)]
Placebo	10.9 ± 3.4 (88) 10.5 (6, 19)	8.0 ± 4.5 (85) 8.0 (0, 20)	-2.30 ± 0.44		
Zilucoplan 0.3 mg/kg	10.3 ± 2.5 (86) 10.0 (6, 16)	5.6 ± 4.0 (84) 4.5 (0, 14)	-4.39 ± 0.45	-2.09 [-3.24, -0.95]	<0.001

a) Upper row, Mean ± standard deviation (N); Lower row, Median (Min, Max)
b) Least squares mean ± standard error
c) Calculated based on a mixed model repeated measures (MMRM; correlation structure, unstructured) with treatment, baseline MG-ADL total score, baseline QMG total score, geographical region (North America, Europe, or East Asia), treatment-by-time interaction, and baseline MG-ADL total score-by-time interaction as factors.
d) Difference between groups in mean change from baseline

Table 46 shows the incidence of any adverse event and the incidence of adverse events occurring in ≥5% of subjects in either group.

Table 46. Incidence of any adverse event and incidence of adverse events occurring in ≥5% of subjects in either group (safety analysis set)

	Placebo (N = 88)	Zilucoplan 0.3 mg/kg (N = 86)
Any adverse event	62 (70.5)	66 (76.7)
Adverse events occurring in ≥5% of subjects in either group		
Injection site bruising	8 (9.1)	14 (16.3)
Headache	14 (15.9)	13 (15.1)
Myasthenia gravis	8 (9.1)	9 (10.5)
Diarrhoea	2 (2.3)	9 (10.5)
Injection site pain	3 (3.4)	8 (9.3)
Urinary tract infection	4 (4.5)	7 (8.1)
Contusion	3 (3.4)	7 (8.1)
Lipase increased	1 (1.1)	7 (8.1)
Nasopharyngitis	3 (3.4)	5 (5.8)
Amylase increased	2 (2.3)	5 (5.8)
Vomiting	5 (5.7)	3 (3.5)
Rash	5 (5.7)	3 (3.5)

n (%)

26) In the primary analysis, intercurrent events during the study period were handled as follows:
- Rescue therapy: subjects are assumed to be treatment failure after the use of rescue therapy.
- Death or myasthenic crisis: subjects are assumed to be treatment failure from the time of death or myasthenic crisis.
- Other monotone missing data: it is assumed that the subject had remained on assigned study drug throughout the study.

According to the principle of handling of intercurrent events above, the protocol specified that data were to be handled as follows:
- Data collected after rescue therapy, subject's death, or onset of myasthenic crisis will be censored. The censored data will be handled as missing data, which will be imputed by the baseline or the last available score (including unscheduled visit) whichever is worse.
- Other monotone missing data will not be imputed.

27) A scale system that assesses 8 items for MG symptoms, i.e., ocular muscles (2 items = double vision and ptosis), bulbar symptoms (3 items = talking, chewing, and swallowing), respiratory muscles (1 item = breathing), and gross motor/limb muscles (2 items = impairment of ability to brush teeth or comb hair and impairment of ability to rise from a chair), each scored on a 4-point scale from 0 (normal) to 3 (severe), rated by assessors based on patients' report.

Death occurred in 1 subject in the placebo group (cerebral haemorrhage) and 1 subject in the zilucoplan 0.3 mg/kg group (COVID-19 and COVID-19 pneumonia). A causal relationship to the study drug was ruled out for these events. Table 47 shows serious adverse events other than death. Adverse events led to treatment discontinuation in 2.3% (2 of 88) of subjects in the placebo group (cerebral haemorrhage and hyperemesis gravidarum [1 subject each]) and 4.7% (4 of 86) of subjects in the zilucoplan group (aphthous ulcer, mouth ulceration, COVID-19, and hepatic enzyme increased [1 subject each]). A causal relationship to the study drug was ruled out for these events except for aphthous ulcer (1 subject) in the zilucoplan group.

Table 47. Serious adverse events other than death (safety analysis set)

Placebo	Serious adverse events reported in a total of 12 subjects: myasthenia gravis (5 subjects); herpes simplex meningoencephalitis[a)]/metastases to meninges[a)]/cerebrovascular accident (1 subject); COVID-19/COVID-19 pneumonia (1 subject); COVID-19 (1 subject); COVID-19 pneumonia (1 subject); vomiting (1 subject); chronic obstructive pulmonary disease (1 subject); hyperemesis gravidarum (1 subject)
Zilucoplan 0.3 mg/kg	Serious adverse events reported in a total of 10 subjects: myasthenia gravis (1 subject); oesophageal candidiasis/oral candidiasis[a)] (1 subject); myasthenia gravis/pneumonia (1 subject); sepsis (1 subject); anaemia (1 subject); aphthous ulcer[a)] (1 subject); lipase increased[a)] (1 subject); basal cell carcinoma (1 subject); pulmonary embolism (1 subject); angioedema[a)] (1 subject)

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

7.3.2 Global long-term extension study (CTD 5.3.5.2.1 and 5.3.5.2.2, Study MG0011 [ongoing since December 2019, data cut-off on [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted to evaluate the long-term safety, tolerability, and efficacy of zilucoplan in patients who completed the foreign phase II study (Study MG0009) or the global phase III study (Study MG0010) (target sample size, approximately 200 subjects).

Subjects were to receive zilucoplan subcutaneously once daily. The dose of zilucoplan was to be determined based on Table 44.

The treatment groups in Study MG0011 were defined as shown in Table 48 based on treatments in the previous study in which subjects participated (Study MG0009 or MG0010).

Table 48. Treatment groups in Study MG0011

Treatment group	Treatment groups in previous studies		
	MG0009		MG0010
	Main portion	Extension portion	
Placebo / zilucoplan 0.1 mg/kg / zilucoplan 0.3 mg/kg	Placebo	Zilucoplan 0.1 mg/kg	—
Placebo / zilucoplan 0.3 mg/kg	Placebo	Zilucoplan 0.3 mg/kg	—
	—	—	Placebo
Zilucoplan 0.1 mg/kg / zilucoplan 0.1 mg/kg / zilucoplan 0.3 mg/kg	Zilucoplan 0.1 mg/kg	Zilucoplan 0.1 mg/kg	—
Zilucoplan 0.3 mg/kg / zilucoplan 0.3 mg/kg	Zilucoplan 0.3 mg/kg	Zilucoplan 0.3 mg/kg	—
	—	—	Zilucoplan 0.3 mg/kg

All 200 enrolled subjects (5 subjects [placebo / zilucoplan 0.1 mg/kg / zilucoplan 0.3 mg/kg], 90 subjects [placebo / zilucoplan 0.3 mg/kg], 12 subjects [zilucoplan 0.1 mg/kg / zilucoplan 0.1 mg/kg / zilucoplan 0.3 mg/kg], and 93 subjects [zilucoplan 0.3 mg/kg / zilucoplan 0.3 mg/kg]) were included in the safety analysis set and the mITT population. The mITT population was the population used for efficacy analyses. Treatment discontinuation occurred in 34 subjects (1 subject in the placebo / zilucoplan 0.1 mg/kg / zilucoplan 0.3 mg/kg group, 21 subjects in the placebo / zilucoplan 0.3 mg/kg group, 1 subject in the zilucoplan 0.1 mg/kg

/ zilucoplan 0.1 mg/kg / zilucoplan 0.3 mg/kg group, and 11 subjects in the zilucoplan 0.3 mg/kg / zilucoplan 0.3 mg/kg group), and the common reasons for treatment discontinuation were summarized. Treatment was discontinued in 12 subjects due to "withdrawal of consent" (0 subjects, 10 subjects, 1 subject, and 1 subject, respectively), 6 subjects due to "adverse events" (0 subjects, 5 subjects, 0 subjects, and 1 subject, respectively), 6 subjects due to "investigator's decision" (0 subjects, 4 subjects, 0 subjects, and 2 subjects, respectively), and 5 subjects due to "death" (0 subjects, 1 subject, 0 subjects, and 4 subjects, respectively).

Table 49 shows the change from the previous study's baseline (Study MG0009 or MG0010) in MG-ADL total score at each timepoint, the efficacy endpoint.

Table 49. Change from the previous study's baseline in MG-ADL total score at each timepoint (mITT population)

		Placebo / zilucoplan 0.3 mg/kg			Zilucoplan 0.3 mg/kg / zilucoplan 0.3 mg/kg		
		N	Total score[a)]	Change from baseline[b), c)]	N	Total score[a)]	Change from baseline[b), c)]
Previous study	Baseline	90	10.7 ± 3.4	—	93	9.9 ± 2.6	—
	Week 1	90	9.0 ± 3.6	-1.40 ± 0.62	91	7.3 ± 3.6	-2.23 ± 0.49
	Week 2	88	8.4 ± 3.8	-1.96 ± 0.64	93	6.5 ± 3.6	-3.01 ± 0.50
	Week 4	89	8.3 ± 4.1	-2.14 ± 0.66	93	5.8 ± 3.5	-3.73 ± 0.50
	Week 8	90	7.8 ± 4.4	-2.60 ± 0.66	93	5.5 ± 3.8	-4.03 ± 0.53
	Week 12	90	7.8 ± 4.5	-2.61 ± 0.68	93	5.2 ± 3.9	-4.30 ± 0.53
MG0011	Week 1	87	5.3 ± 4.1	-5.96 ± 0.86	91	5.1 ± 4.0	-4.61 ± 0.58
	Week 2	89	4.9 ± 4.1	-6.41 ± 0.87	92	4.4 ± 3.5	-5.13 ± 0.54
	Week 4	89	4.9 ± 4.5	-6.44 ± 0.88	90	4.2 ± 3.4	-5.37 ± 0.55
	Week 8	88	4.4 ± 4.1	-6.83 ± 0.86	90	3.6 ± 3.2	-5.85 ± 0.53
	Week 12	86	4.5 ± 4.0	-6.67 ± 0.86	89	3.7 ± 3.2	-5.77 ± 0.54

a) Mean ± standard deviation
b) Least squares mean ± standard error
c) Calculated based on an MMRM (correlation structure, unstructured) with baseline MG-ADL total score, baseline QMG total score, geographical region (North America, Europe, or East Asia), previous study, baseline MG-ADL total score-by-time interaction as factors.

Table 50 shows the incidence of any adverse event and the incidence of adverse events occurring in ≥5% of subjects in any group.

Table 50. Incidence of any adverse event and incidence of adverse events occurring in ≥5% of subjects in any group (safety analysis set)

	Placebo / zilucoplan 0.1 mg/kg / zilucoplan 0.3 mg/kg (N = 5)	Placebo / zilucoplan 0.3 mg/kg (N = 90)	Zilucoplan 0.1 mg/kg / zilucoplan 0.1 mg/kg / zilucoplan 0.3 mg/kg (N = 12)	Zilucoplan 0.3 mg/kg / zilucoplan 0.3 mg/kg (N = 93)
Any adverse event	5 (100)	86 (95.6)	12 (100)	85 (91.4)
Adverse events occurring in ≥5% of subjects in any group				
Myasthenia gravis	2 (40.0)	21 (23.3)	5 (41.7)	24 (25.8)
COVID-19	1 (20.0)	20 (22.2)	4 (33.3)	24 (25.8)
Diarrhoea	2 (40.0)	9 (10.0)	2 (16.7)	17 (18.3)
Headache	2 (40.0)	14 (15.6)	4 (33.3)	15 (16.1)
Nasopharyngitis	0	10 (11.1)	6 (50.0)	14 (15.1)
Arthralgia	2 (40.0)	10 (11.1)	3 (25.0)	13 (14.0)
Nausea	1 (20.0)	14 (15.6)	2 (16.7)	12 (12.9)
Pain in extremity	2 (40.0)	8 (8.9)	1 (8.3)	12 (12.9)
Fatigue	0	10 (11.1)	2 (16.7)	10 (10.8)
Urinary tract infection	2 (40.0)	10 (11.1)	2 (16.7)	9 (9.7)
Vomiting	3 (60.0)	4 (4.4)	2 (16.7)	9 (9.7)
Upper respiratory tract infection	3 (60.0)	11 (22.2)	1 (8.3)	8 (8.6)
Back pain	2 (40.0)	8 (8.9)	1 (8.3)	8 (8.6)
Depression	1 (20.0)	6 (6.7)	0	8 (8.6)
Muscle spasms	1 (20.0)	5 (5.6)	0	8 (8.6)
Cough	2 (40.0)	7 (7.8)	2 (16.7)	7 (7.5)
Rash	0	6 (6.7)	2 (16.7)	7 (7.5)
Fall	1 (20.0)	7 (7.8)	2 (16.7)	6 (6.5)
Sinusitis	0	3 (3.3)	1 (8.3)	6 (6.5)
Lipase increased	2 (40.0)	5 (5.6)	0	6 (6.5)
Dyspnoea	1 (20.0)	6 (6.7)	2 (16.7)	5 (5.4)
Abdominal pain	2 (40.0)	5 (5.6)	1 (8.3)	5 (5.4)
Pyrexia	0	4 (4.4)	2 (16.7)	5 (5.4)
Insomnia	0	3 (3.3)	2 (16.7)	5 (5.4)
Oedema peripheral	1 (20.0)	5 (5.6)	1 (8.3)	4 (4.3)
Injection site pain	0	5 (5.6)	1 (8.3)	4 (4.3)
Myalgia	1 (2.0)	5 (5.6)	0	4 (4.3)
Dizziness	2 (40.0)	4 (4.4)	2 (16.7)	4 (4.3)
Injection site bruising	0	10 (11.1)	4 (33.3)	3 (3.2)
Oropharyngeal pain	0	8 (8.9)	1 (8.3)	1 (1.1)

n (%)

Death occurred in 4 subjects (0 subjects [placebo / zilucoplan 0.1 mg/kg / zilucoplan 0.3 mg/kg], 1 subject [death; placebo / zilucoplan 0.3 mg/kg], 0 subjects [zilucoplan 0.1 mg/kg / zilucoplan 0.1 mg/kg / zilucoplan 0.3 mg/kg], and 3 subjects [cardiac arrest in 2 subjects and head injury in 1 subject; zilucoplan 0.3 mg/kg / zilucoplan 0.3 mg/kg]). A causal relationship to the study drug was ruled out for all events. Table 51 shows serious adverse events other than death. Adverse events led to treatment discontinuation in 11.1% (10 of 90) of subjects in the placebo / zilucoplan 0.3 mg/kg group (myasthenia gravis [3 subjects], myasthenia gravis crisis [1 subject], death [1 subject], injection site bruising [1 subject], injection site pain [1 subject], injection site rash [1 subject], abdominal distension [1 subject], diarrhoea [1 subject], flatulence [1 subject], gastrointestinal haemorrhage [1 subject], haematochezia [1 subject], intestinal perforation [1 subject], nausea [1 subject], stomatitis [1 subject], abdominal infection [1 subject], diverticulitis [1 subject], enterococcal bacteraemia [1 subject], eyelid abrasion [1 subject], skin abrasion [1 subject], skin injury [1 subject], skin laceration [1 subject], acute kidney injury [1 subject], bladder spasm [1 subject], renal dysfunction [1 subject], neutropenia [1 subject], keratitis [1 subject], lipase increased [1 subject], folate deficiency [1 subject], back pain [1 subject], acute respiratory failure [1 subject], haemoptysis [1 subject]) and 7.5% (7 of 93) of subjects in the zilucoplan 0.3 mg/kg / zilucoplan 0.3 mg/kg group (cardiac arrest [2 subjects], myasthenia gravis [2 subjects], ischaemic stroke [1 subject], endocarditis candida [1 subject], head injury [1 subject]). A causal relationship to the study drug was ruled out for the above events except for the

following events in the placebo / zilucoplan 0.3 mg/k group: renal dysfunction (1 subject), injection site pain (1 subject), injection site bruising (1 subject), injection site rash (1 subject), neutropenia (1 subject), and lipase increased (1 subject).

Table 51. Serious adverse events other than death (safety analysis set)

Placebo / zilucoplan 0.1 mg/kg / zilucoplan 0.3 mg/kg	Serious adverse events reported in a total of 4 subjects: abdominal pain/back pain/gastric ulcer (1 subject); osteoarthritis (1 subject); abdominal pain (1 subject); diverticulitis (1 subject)
Placebo / zilucoplan 0.3 mg/kg	Serious adverse events reported in a total of 22 subjects: myasthenia gravis (5 subjects); epididymitis[a)]/Klebsiella infection[a)] (1 subject); abdominal infection/back pain/diverticulitis/enterococcal bacteraemia/gastrointestinal haemorrhage (1 subject); acute respiratory failure/heart injury/pneumonia legionella (1 subject); coronary artery disease/myasthenia gravis crisis/sepsis (1 subject); cholecystitis/coronary artery stenosis/inflammation (1 subject); blood glucose fluctuation/bursitis/prostatitis (1 subject); cerebrovascular accident/herpes simplex meningoencephalitis/meningeal disorder[a)] (1 subject); myasthenia gravis crisis/pneumonia aspiration (1 subject); cardiac failure/renal dysfunction (1 subject); amnesia/syncope (1 subject); metastatic malignant melanoma (1 subject); abortion induced (1 subject); cellulitis (1 subject); acute respiratory failure/COVID-19/COVID-19 pneumonia (1 subject); metastatic neoplasm (1 subject); large intestine polyp (1 subject); renal failure (1 subject)
Zilucoplan 0.1 mg/kg / zilucoplan 0.1 mg/kg / zilucoplan 0.3 mg/kg	Serious adverse events reported in a total of 3 subjects: bile duct stenosis/COVID-19/cholangitis/cholecystitis infective/hepatitis C/pancreatitis/pneumonia/post procedural haemorrhage/post procedural sepsis/pulseless electrical activity/sepsis (1 subject); COVID-19 pneumonia/viral infection (1 subject); bradycardia (1 subject)
Zilucoplan 0.3 mg/kg / zilucoplan 0.3 mg/kg	Serious adverse events reported in a total of 31 subjects: myasthenia gravis (6 subjects); acetabulum fracture/anaemia/atrial fibrillation/carotid artery thrombosis/embolic stroke/heart rate irregular/myocardial infarction/orthostatic hypotension/rib fracture/spinal compression fracture/spinal fracture (1 subject); bacteraemia/endocarditis candida (1 subject); pancreatic mass/transaminases increased (1 subject); cardiac failure/injection site infection[a)]/ myasthenia gravis (1 subject); bone neoplasm/COVID-19 pneumonia/staphylococcal infection (1 subject); infection/myasthenia gravis/vomiting (1 subject); cellulitis/hip fracture (1 subject); delayed recovery from anaesthesia/myasthenia gravis (1 subject); angina pectoris (1 subject); COVID-19 pneumonia (1 subject); myocardial infarction/pulmonary embolism (1 subject); fall (1 subject); uterine leiomyoma (1 subject); COVID-19 (1 subject); pneumonia (1 subject); cellulitis (1 subject); oesophageal stenosis (1 subject); influenza (1 subject); abdominal hernia (1 subject); ovarian cyst (1 subject); ischaemic stroke (1 subject); bronchitis (1 subject); oesophagitis[a)] (1 subject); cholecystitis (1 subject); haematoma muscle (1 subject)

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

7.R Outline of the review conducted by PMDA

7.R.1 Appropriateness of study design of the phase III study

PMDA asked the applicant to explain the study design of the phase III study of zilucoplan.

The applicant's explanation:

- In and outside Japan, MG is diagnosed based on medical history, symptoms, pathogenic autoantibodies, and the assessment of neuromuscular junction impairment by electrophysiological tests (e.g., repetitive nerve stimulation test and single fiber electromyography) and other tests (MG Clinical Guidelines, *Nat Rev Dis Primers.* 2019;5:30). The first-line therapies for gMG include acetylcholinesterase inhibitors, oral corticosteroids, and immunosuppressants, alone or combined, depending on the symptoms and condition of the patient. For patients who responded inadequately to these therapies, intravenous immunoglobulin (IVIg), plasmapheresis, or molecular targeted therapies (anti-C5 antibody, anti-FcRn antibody) are used. In patients with MG accompanied by thymoma or thymic hyperplasia, thymectomy is performed. The gMG treatment algorithm in Japan does not differ significantly from that in other countries. Furthermore, the phase I study in healthy Japanese and non-Japanese adults (Study UP0113) demonstrated no clear differences in the pharmacokinetics of unchanged zilucoplan and its metabolites between the Japanese and non-Japanese populations [see Section 6.R.1]. The above results suggest that intrinsic and extrinsic ethnic factors are unlikely to affect the efficacy and safety evaluation of zilucoplan. Accordingly, the phase III study (Study MG0010) was conducted as a global study including Japan.

- The primary endpoint for Study MG0010 was the change from baseline in MG-ADL total score, an 8-item scale assessed by the investigator based on the patient's self-report to determine the severity of MG symptoms using the sum of individual scores. The scale system has been used widely in clinical studies involving patients with gMG in and outside Japan (*Muscle Nerve.* 2011;44:727-31, *Muscle Nerve*. 2022;65:630-9). The secondary endpoints included change from baseline in the QMG total score in the severity of gMG by function (ocular/facial muscles, bulbar symptoms, gross motor/axial muscles, and respiratory muscles).
- In Study MG0009, the change from baseline in QMG total score and that in MG-ADL total score remained at similar levels at and after Week 8. Based on the results of Study MG0009 and other data, Study MG0010 also used Week 12 as the timepoint for assessment of the primary endpoint.
- In Study MG0010, eligible patients were those with gMG as diagnosed by the MGFA Clinical Classification (Class II to IV), with specified severity according to the MG-ADL and QMG scores, regardless of prior therapy. It was assumed that the criteria would not allow enrollment of patients with mild gMG whose symptoms were likely to improve only with low-dose oral corticosteroids or acetylcholinesterase inhibitors. Zilucoplan is expected to have pharmacological effects on the complement cascade, which is activated by anti-AChR antibodies; therefore, patients who were anti-AChR antibody positive were defined as eligible.
- In Study MG0009, the results for the primary endpoint, the change from baseline in QMG total score at Week 12 (Table 39) as well as the secondary endpoints, the changes from baseline in MG-ADL and Myasthenia Gravis Composite (MGC) total scores at Week 12, showed that the changes were higher in both of the zilucoplan dose groups than in the placebo group, and the changes tended to be higher in the 0.3 mg/kg group than in the 0.1 mg/kg group. Based on various factors including the above results, the dosage (Table 44) corresponding to zilucoplan 0.3 mg/kg used in Study MG0009 was selected as the dosage for Study MG0010.

PMDA's view:

There is no significant difference in intrinsic or extrinsic ethnic factors among countries or regions that were included in Study MG0010, in which Japanese patients participated. It is reasonable for the applicant to select a development plan using global clinical studies to evaluate the efficacy and safety of zilucoplan. In Study MG0010 conducted as a confirmatory study, change from baseline in MG-ADL total score was adopted as the primary endpoint, which is also reasonable. However, not only the MG-ADL scale, which can be used to assess the level of impairment in activities of daily living, but also QMG, which can detect muscles prone to fatigue with a high degree of sensitivity, are important for evaluating the efficacy of treatment for gMG. Therefore, the efficacy of zilucoplan should be evaluated comprehensively based on the change from baseline in MG-ADL total score, the primary endpoint, and on the QMG total score, the secondary endpoint in Study MG0010.

7.R.2 Efficacy

PMDA asked the applicant to explain the efficacy of zilucoplan.

The applicant's explanation about the efficacy of zilucoplan based on the results of Study MG0010:

Table 45 shows the change from baseline in MG-ADL total score at Week 12, the primary endpoint of Study MG0010. The superiority of zilucoplan over placebo was tested in the study. A reduction in the MG-ADL score indicates improvements in MG symptoms and execution of activities of daily living, and a ≥2-point reduction in MG-ADL total score is defined as the minimal clinically important difference (*Muscle Nerve*. 2011;44:727-31, *Neurology*. 1999;52:1487-9). In Study MG0010, the difference between zilucoplan and placebo in the change from baseline in MG-ADL total score at Week 12 was −2.09 [95% CI: −3.24, −0.95], demonstrating the clinically meaningful efficacy of zilucoplan. In addition, the proportion of subjects achieving a ≥3-point reduction (improvement) in MG-ADL total score from baseline at Week 12, a secondary endpoint, was 73.1% in the zilucoplan group and 46.1% in the placebo group. The change from baseline in MG-ADL total score in the zilucoplan group tended to be consistently higher than that in the placebo group up to Week 12.

Table 53 shows the change from baseline in QMG total score, a secondary endpoint. The change from baseline in QMG total score demonstrated a trend toward improvement in the zilucoplan group compared to placebo.

The efficacy data for the Japanese population are shown in the tables below. The change from baseline at Week 12 in MG-ADL total score (Table 52) and that in QMG total score (Table 53) both showed trends toward improvement in the zilucoplan group compared to placebo, which were consistent with the data from the overall population.

Table 52. Changes from baseline at Week 12 in MG-ADL total score in the overall and Japanese populations in Study MG0010 (mITT population)

	Treatment	MG-ADL total score			
		Baseline[a)]	Week 12[a)]	Change from baseline[b), c)]	Difference between groups in change from baseline [95% CI][c)]
Overall population	Placebo	10.9 ± 3.4 (88) 10.5 (6, 19)	8.0 ± 4.5 (85) 8.0 (0, 20)	-2.30 ± 0.44	—
	Zilucoplan	10.3 ± 2.5 (86) 10.0 (6, 16)	5.6 ± 4.0 (84) 4.5 (0, 14)	-4.39 ± 0.45	-2.09 [-3.24, -0.95]
Japanese population	Placebo	11.0 ± 3.4 (9) 12.0 (6, 17)	10.0 ± 4.4 (9) 8.0 (3, 16)	-0.45 ± 0.98	—
	Zilucoplan	10.7 ± 2.8 (7) 11.0 (7, 14)	6.0 ± 4.2 (7) 7.0 (0, 10)	-4.71 ± 1.12	-4.26 [-7.40, -1.12]

a) Upper row, Mean ± standard deviation (N); Lower row, Median (Min, Max)
b) Least squares mean ± standard error
c) Analysis model: correlation structure, unstructured (overall population), first-order autoregressive (AR[1]) (Japanese population)

Table 53. Changes from baseline at Week 12 in QMG total score in the overall and Japanese populations in Study MG0010 (mITT population)

	Treatment	QMG total score			
		Baseline[a)]	Week 12[a)]	Change from baseline[b), c)]	Difference between groups in change from baseline [95% CI][c)]
Overall population	Placebo	19.4 ± 4.5 (88) 18.5 (13, 36)	16.0 ± 6.0 (84) 16.0 (5, 38)	-3.25 ± 0.55	—
	Zilucoplan	18.7 ± 3.6 (86) 18.0 (12, 31)	12.3 ± 5.4 (83) 12.0 (0, 33)	-6.19 ± 0.56	-2.94 [-4.39, -1.49]
Japanese population	Placebo	18.3 ± 3.0 (9) 18.0 (14, 23)	15.8 ± 5.6 (9) 18.0 (6, 22)	-2.07 ± 1.59	—
	Zilucoplan	17.0 ± 2.0 (7) 18.0 (13, 19)	12.3 ± 5.0 (7) 12.0 (5, 19)	-5.20 ± 1.81	-3.13 [-8.24, -1.98]

a) Upper row, Mean ± standard deviation (N); Lower row, Median (Min, Max)
b) Least squares mean ± standard error
c) Calculated based on the following analysis model:
QMG total score: an MMRM (correlation structure, unstructured for the overall population and AR[1] for the Japanese population) with treatment, baseline MG-ADL total score, baseline QMG total score, geographical region (North America, Europe, or East Asia), treatment-by-time interaction, baseline QMG total score-by-time interaction as factors.

Subgroup analyses were performed on the change from baseline in MG-ADL total score by patient characteristics. There was no trend toward difference in efficacy among patient subgroups with specific characteristics.

Furthermore, the change from baseline at Week 12 in subscore of MG-ADL score (Table 54) and that in subscore of QMG score (Table 55) demonstrated a trend toward improvement in the zilucoplan group compared to placebo for all subscores

Table 54. Change from baseline at Week 12 in subscore of MG-ADL score in Study MG0010 (mITT population, observed cases [OC])

Subscore[a)]	Placebo			Zilucoplan		
	Baseline	Week 12	Change from baseline	Baseline	Week 12	Change from baseline
Ocular muscles	3.6 ± 1.6 (88) 4.0 (0, 6)	2.8 ± 2.0 (85) 2.0 (0, 6)	-0.84 ± 1.56 (85) 0.0 (-5.0, 3.0)	3.3 ± 1.5 (86) 3.0 (0, 6)	1.8 ± 1.7 (84) 1.0 (0, 6)	-1.44 ± 1.69 (84) -1.0 (-6.0, 3.0)
Gross motor/limb muscles	2.8 ± 1.4 (88) 3.0 (0, 6)	2.1 ± 1.5 (85) 2.0 (0, 6)	-0.71 ± 1.34 (85) 0.0 (-5.0, 2.0)	2.8 ± 1.1 (86) 3.0 (0, 5)	1.6 ± 1.5 (84) 1.5 (0, 5)	-1.15 ± 1.44 (84) -1.0 (-4.0, 2.0)
Respiratory muscles	1.1 ± 0.6 (88) 1.0 (0, 2)	0.9 ± 0.7 (85) 1.0 (0, 2)	-0.22 ± 0.70 (85) 0.0 (-2.0, 1.0)	1.1 ± 0.7 (86) 1.0 (0, 3)	0.8 ± 0.7 (84) 1.0 (0, 2)	-0.33 ± 0.61 (84) 0.0 (-2.0, 1.0)
Bulbar symptoms	3.3 ± 1.8 (88) 3.0 (0, 9)	2.2 ± 2.0 (85) 2.0 (0, 9)	-1.08 ± 1.68 (85) -1.0 (-6.0, 3.0)	3.1 ± 1.5 (86) 3.0 (0, 7)	1.3 ± 1.5 (84) 1.0 (0, 5)	-1.77 ± 1.82 (84) -2.0 (-6.0, 3.0)

Upper row, Mean ± standard deviation (N); Lower row, Median (Min, Max)
a) Ocular muscles: double vision and ptosis
Gross motor/limb muscles: impairment of ability to brush teeth or comb hair and impairment of ability to rise from a chair
Respiratory muscles: breathing
Bulbar symptoms: talking, chewing, and swallowing

Table 55. Change from baseline at Week 12 in subscore of QMG score in Study MG0010 (mITT population, OC)

Subscore[a)]	Placebo			Zilucoplan		
	Baseline	Week 12	Change from baseline	Baseline	Week 12	Change from baseline
Ocular/ facial muscles	5.1 ± 2.1 (88) 5.0 (0, 9)	3.8 ± 2.4 (84) 4.0 (0, 9)	-1.24 ± 2.17 (84) -1.0 (-9.0, 3.0)	4.8 ± 2.0 (86) 5.0 (0, 8)	2.8 ± 2.1 (83) 3.0 (0, 8)	-1.98 ± 2.16 (83) -2.0 (-7.0, 2.0)
Gross motor/ axial muscles	11.4 ± 2.6 (88) 12.0 (4, 21)	10.2 ± 3.6 (84) 10.0 (1, 21)	-1.21 ± 2.41 (84) -1.0 (-10.0, 3.0)	11.1 ± 2.1 (86) 11.0 (5, 19)	8.3 ± 3.3 (83) 8.0 (0, 19)	-2.87 ± 2.59 (83) -3.0 (-9.0, 3.0)
Respiratory muscles	0.9 ± 1.0 (88) 1.0 (0, 3)	0.8 ± 1.0 (84) 0 (0, 3)	-0.11 ± 0.71 (84) 0 (-2.0, 2.0)	0.8 ± 1.0 (86) 0 (0, 3)	0.5 ± 0.8 (83) 0 (0, 3)	-0.24 ± 0.62 (83) 0 (-3.0, 1.0)
Bulbar symptoms	2.0 ± 1.6 (88) 2.0 (0, 6)	1.1 ± 1.5 (84) 0 (0, 6)	-0.86 ± 1.45 (84) -1.0 (-4.0, 3.0)	2.0 ± 1.5 (86) 2.0 (0, 5)	0.7 ± 1.1 (83) 0 (0, 5)	-1.23 ± 1.48 (83) -1.0 (-5.0, 2.0)

Upper row, Mean ± standard deviation (N); Lower row, Median (Min, Max)

a) Ocular/facial muscles: double vision, ptosis, facial muscles
Gross motor/axial muscles: right and left hand grip, arms outstretched, legs outstretched, head lifted
Respiratory muscles: forced vital capacity
Bulbar symptoms: swallowing 4 oz of water, speech after counting aloud from 1 to 50

The long-term efficacy of zilucoplan (>12 weeks) was analyzed using pooled data from Studies MG0009, MG0010, and MG0011 (Pool E2 data[28)]). Table 56 shows change over time from baseline in MG-ADL total score in subjects who received zilucoplan 0.3 mg/kg in the double-blind period and also received zilucoplan 0.3 mg/kg in the open-label period. The MG-ADL score continued to improve throughout the treatment period.

Table 56. Change over time from baseline in MG-ADL total score in Pool E2 data (safety analysis set)

	Zilucoplan 0.3 mg/kg (double-blind)/ zilucoplan 0.3 mg/kg (open-label)	Change from baseline
Baseline	9.9 ± 2.7 (100)	—
Week 1	7.3 ± 3.6 (98)	-2.6 ± 3.1
Week 2	6.5 ± 3.6 (100)	-3.4 ± 3.4
Week 4	5.8 ± 3.5 (99)	-4.1 ± 3.4
Week 8	5.5 ± 3.8 (97)	-4.4 ± 3.8
Week 12	5.4 ± 4.0 (97)	-4.5 ± 3.9
Week 13	5.1 ± 4.0 (93)	-4.9 ± 4.0
Week 14	4.4 ± 3.4 (94)	-5.4 ± 3.4
Week 16	4.2 ± 3.4 (92)	-5.5 ± 3.5
Week 20	3.6 ± 3.2 (92)	-6.2 ± 3.5
Week 24	3.7 ± 3.2 (91)	-6.2 ± 3.7
Week 36	3.3 ± 3.3 (86)	-6.6 ± 3.6
Week 48	3.1 ± 3.4 (87)	-6.8 ± 3.5
Week 60	4.0 ± 4.2 (60)	-6.0 ± 4.1
Week 72	4.1 ± 4.5 (47)	-5.8 ± 4.3
Week 84	3.4 ± 3.5 (40)	-6.3 ± 3.9
Week 96	3.4 ± 3.3 (32)	-5.8 ± 3.6

Mean ± standard deviation (N)

The applicant considers that the above data have demonstrated the efficacy of zilucoplan in patients with gMG.

PMDA's view:

In Study MG0010, the results for the primary endpoint, the change from baseline in MG-ADL total score at Week 12, demonstrated the superiority of zilucoplan over placebo. The results for the change from baseline in QMG total score at Week 12, a secondary endpoint, demonstrated a trend toward improvement in the zilucoplan group compared to placebo. Although only a limited number of Japanese patients were included in

28) Pooled efficacy data in all patients with gMG from Studies MG0009, MG0010, and MG0011 (data cut-off on [redacted], 20[redacted]) including long-term data.

Study MG0010, there was no trend toward a difference between the Japanese population and the overall population. The Pool E2 data showed that zilucoplan tended to remain effective throughout the treatment period.

The above findings support the efficacy of zilucoplan in Japanese patients with gMG.

7.R.3 Safety

The submitted data were reviewed on the safety of zilucoplan, and the details are presented in Sections 7.R.3.1 through 7.R.3.8. In light of the results of the review, PMDA reached the following conclusion: Patients being treated with zilucoplan should be closely monitored for the risks of infections including those caused by *Neisseria meningitidis* and other encapsulated bacteria, increases in pancreatic enzymes, pancreatitis, and serious hypersensitivity reactions; however, zilucoplan has acceptable safety in Japanese patients with gMG in view of the demonstrated efficacy, provided that zilucoplan is only used under the supervision of a physician who is familiar with the diagnosis and treatment of gMG and is also fully capable of managing the risks associated with the use of zilucoplan, such as meningococcal infection, at a medical institution that can respond to such risks.

7.R.3.1 Adverse events reported in clinical studies

PMDA asked the applicant to explain the safety of zilucoplan in patients with gMG.

The applicant's explanation about the safety of zilucoplan based on the results from studies including Studies MG0009, MG0010, and MG0011:

Table 57 summarizes the safety based on the pooled data from Studies MG0009 (main portion) and MG0010 (hereinafter referred to as "gMG double-blind pooled data") and pooled data from Studies MG0009 (overall study period), MG0010, and MG0011 (data cut-off on [redacted], 20[redacted]) (hereinafter referred to as "gMG overall pooled data"). In the gMG double-blind pooled data, the incidence of adverse events tended to be higher in the zilucoplan group than in the placebo group, while the incidences of serious adverse events and adverse events leading to treatment discontinuation in the zilucoplan group were similar to those in the placebo group. The most common serious adverse events reported in the zilucoplan group were events coded to System Organ Class (SOC) "infections and infestations." In the gMG double-blind pooled data, the only adverse event occurring at a ≥5% higher incidence in the zilucoplan group than in the placebo group was diarrhoea (9.6% [11 of 115 subjects] in the zilucoplan group and 2.9% [3 of 103 subjects] in the placebo group). All events of diarrhoea were classified as non-serious and none of the events led to treatment discontinuation.

Table 57. Summary of adverse events: pooled data (safety analysis set)

	gMG double-blind period pooled data		gMG overall pooled data
	Placebo	Zilucoplan	
N	103	115	213
Any adverse event	76 (73.8)	93 (80.9)	204 (95.8)
Death	1 (1.0)	1 (0.9)	8 (3.8)
Serious adverse events	16 (15.5)	16 (13.9)	78 (36.6)
Adverse events leading to treatment discontinuation	2 (1.9)	4 (3.5)	24 (11.3)

n (%)

Table 58 shows the incidence of adverse events in the Japanese and overall populations in Study MG0010. Although the limited number of Japanese subjects precludes a stringent comparison, there were no significant differences between the populations.

Table 58. Incidence of common adverse events in the Japanese and overall populations in Study MG0010 (safety analysis set)

	Overall population		Japanese population	
	Placebo	Zilucoplan	Placebo	Zilucoplan
N	N = 88	N = 86	N = 9	N = 7
Any adverse event	62 (70.5)	66 (76.7)	5 (55.6)	4 (57.1)
Death	1 (1.1)	1 (1.2)	0	0
Serious adverse events	13 (14.8)	11 (12.8)	3 (33.3)	1 (14.3)
Adverse events leading to treatment discontinuation (including death)	2 (2.3)	4 (4.7)	0	0
Adverse events for which a causal relationship could not be ruled out	22 (25.0)	28 (32.6)	3 (33.3)	0
Severe events	11 (12.5)	10 (11.6)	2 (22.2)	0
Adverse events occurring in ≥5% in any group				
Injection site bruising	8 (9.1)	14 (16.3)	1 (11.1)	0
Headache	14 (15.9)	13 (15.1)	0	1 (14.3)
Myasthenia gravis	8 (9.1)	9 (10.5)	3 (33.3)	0
Diarrhoea	2 (2.3)	9 (10.5)	0	0
Injection site pain	3 (3.4)	8 (9.3)	0	0
Urinary tract infection	4 (4.5)	7 (8.1)	0	0
Contusion	3 (3.4)	7 (8.1)	0	0
Lipase increased	1 (1.1)	7 (8.1)	0	0
Nasopharyngitis	3 (3.4)	5 (5.8)	0	0
Amylase increased	2 (2.3)	5 (5.8)	0	0
Muscle spasms	4 (4.5)	4 (4.7)	0	0
Nausea	1 (1.1)	4 (4.7)	0	0
Oedema peripheral	1 (1.1)	4 (4.7)	0	0
Sinusitis	0	4 (4.7)	0	0
Pyrexia	0	4 (4.7)	0	1 (14.3)
Vomiting	5 (5.7)	3 (3.5)	0	0
Rash	5 (5.7)	3 (3.5)	0	0
Chest pain	1 (1.1)	1 (1.2)	0	1 (14.3)
Hypoglycaemia	0	1 (1.2)	0	1 (14.3)
Basal cell carcinoma	0	1 (1.2)	0	1 (14.3)
Injection site rash	2 (2.3)	0	1 (11.1)	0
Lymphocyte count decreased	3 (3.4)	0	1 (11.1)	0
Musculoskeletal disorder	1 (1.1)	0	1 (11.1)	0
Ingrowing nail	1 (1.1)	0	1 (11.1)	0

n (%)

PMDA's view:

Because there was no trend toward significant difference between the Japanese population and the overall population in the incidence of adverse events in Study MG0010, the safety of zilucoplan in Japanese patients with gMG can be evaluated based on the submitted data on the overall population in the clinical studies.

Infection-related adverse events, pancreatic adverse events, adverse events related to hypersensitivity reactions, malignancy-related adverse events, adverse events associated with skin and oral mucosal ulceration, hepatic dysfunction-related adverse events, and elevation of eosinophil count will be discussed in detail in Section 7.R.3.2 and subsequent sections [see Sections 7.R.3.2 to 7.R.3.8] based on the incidence of adverse events in the clinical studies, findings reported in the non-clinical studies, the pharmacology and route of administration of zilucoplan.

With the exception of the adverse events listed above, no adverse events reported during treatment with zilucoplan have raised concerns that could be problematic in clinical settings, given the incidence and severity of adverse events and other data in the clinical studies.

7.R.3.2 Infection-related adverse events

7.R.3.2.1 Meningococcal infection and other encapsulated bacterial infections

PMDA asked the applicant to explain the risks of infections caused by *Neisseria meningitidis* and other encapsulated bacteria in patients being treated with zilucoplan, as well as the safety measures to reduce the incidence of such infections and prevent severe infections.

The applicant's explanation about meningococcal infection:
Since *Neisseria* bacteria are mainly eliminated by terminal complement components, defects of terminal complement components are associated with an increased risk of infections caused by genus *Neisseria* (particularly *Neisseria meningitidis*) (*FEBS Letter*. 2020;594:2670-94, *Molecular Immunology*. 2011;48:1643-55). Meningococcal infections have been reported in patients being treated with other C5 inhibitors, eculizumab and ravulizumab, approved in Japan (package insert of "Soliris for Intravenous Infusion 300 mg," Fifth revision, revised in June 2023; and package insert of "Ultomiris for Intravenous Infusion 300 mg and other dosage," Eighth revision, revised in June 2023). There was a concern about the risk of meningococcal infections associated with the use of zilucoplan, as is the case of eculizumab and ravulizumab (genetical recombination). Therefore, the protocols of the clinical studies in patients with gMG required participants to be vaccinated against *Neisseria meningitidis* prior to the start of treatment with zilucoplan (quadrivalent meningococcal vaccine or serogroup B meningococcal vaccine depending on the standard of the country or region where the study was conducted). Consequently, none of the 724 participants in the clinical studies of zilucoplan conducted in patients with gMG or other diseases had meningococcal infections by the data cut-off date ([redacted], 20[redacted]).

Given the results, in principle, patients need to be vaccinated against *Neisseria meningitidis* before the initiation of treatment with zilucoplan in clinical practice, as implemented in the clinical studies. In accordance with the international recommendations (e.g., *MMWR Recomm Rep.* 2020;69:1-41) for use of meningococcal vaccines for patients who are to receive C5 inhibitors, physicians should be advised to ensure that patients are vaccinated at least 2 weeks before the start of treatment with zilucoplan.

In addition, patients with gMG are expected to receive zilucoplan over a long period of time. Routine booster vaccination with meningococcal vaccine is recommended for patients receiving complement inhibitors (Advisory Committee on Immunization Practices recommendations for the use of quadrivalent meningococcal vaccines in the US) and also for patients including those with persistent complement deficiency (Vaccine Guidelines for Healthcare Professionals [in Japanese]. Third edition. Japanese Society for Infection Prevention and Control;2020). Therefore, physicians should be advised to consider booster vaccination with a meningococcal vaccine in patients being treated with zilucoplan, as necessary.

Furthermore, meningococcal infection may lead to life-threatening outcomes; therefore, as is the case of approved C5 inhibitors, the following important issues (1), (2), and (3) should be included in cautionary statements: (1) zilucoplan should be used under the supervision of a physician familiar with the treatment of gMG at a medical institution that can respond to emergency situations in coordination with other medical institutions that can diagnose and treat meningococcal infection; (2) the patient being treated with zilucoplan should be monitored closely for initial signs of meningococcal infection (e.g., pyrexia, headache, and nuchal rigidity), and appropriate treatment should be provided for the patient immediately if meningococcal infection is suspected; and (3) the patient and the caregiver should be informed of the seriousness of meningococcal infection, and the patient should be instructed to contact the primary care physician if any symptoms related to meningococcal infection arise.

The risk for meningococcal infection associated with the use of zilucoplan is considered manageable by implementing the above safety measures.

The applicant's explanation about infections caused by encapsulated bacteria other than *Neisseria meningitidis*:
Deficiency of complement components (C1 through C4) has been reported to be associated with an increased risk of infections caused by encapsulated bacteria other than *Neisseria meningitidis* (*FEBS Lett.* 2020;594:2670-94, *Mol Immunol.* 2011;48:1643-55). Because zilucoplan is a C5 inhibitor and does not inhibit early complement components, it is unlikely to increase the risk for these infections. No encapsulated bacterial infections were reported in the zilucoplan group in the S2A population,[29)] which is the largest, placebo-controlled pooled analysis set. While precautions for encapsulate bacteria including *Neisseria meningitidis* were included in the package inserts and other information materials for eculizumab and ravulizumab, which are also C5 inhibitors already approved, there is currently no clear evidence supporting the contention that C5 inhibitors increase the risk of encapsulated bacterial infections except for *Neisseria* infections, according to research reports on patients with congenital complement deficiency and data from the clinical studies of eculizumab and ravulizumab (Review Report of "Soliris for Intravenous Infusion 300 mg," dated November 24, 2017, and Review Report of "Ultomiris for Intravenous Infusion 300 mg and other dosage," dated July 14, 2022).

PMDA's view:
Although no meningococcal infections occurred in the clinical studies, there is an increased risk of meningococcal infections associated with the use of zilucoplan, taking into account zilucoplan's mechanism of action, which is similar to other C5 inhibitors that have already been approved. Because meningococcal infections may lead to life-threatening outcome, the following safety measures should be taken, as is the case with the approved C5 inhibitors: (i) before the start of treatment with zilucoplan, patients should be vaccinated against *Neisseria meningitidis*; (ii) patients being treated with zilucoplan should be closely monitored for early

29) Pooled data analysis population comprising double-blind phase data from Study MG0009, Study MG0010, and Study IMNM01 conducted in patients with immune-mediated necrotizing myopathy.

signs for meningococcal infections and appropriate treatment should be provided for the patient immediately if meningococcal infection is suspected; and (iii) zilucoplan should only be used under the supervision of a physician who is fully familiar with the treatment of gMG and is capable of adequately managing the risk of infections including meningococcal infection at a medical institution that can provide the management of such risks. The risk of meningococcal infections associated with the use of zilucoplan can be managed to a certain extent if the above safety measures are implemented.

Although encapsulated bacterial infections except for meningococcal infections were not reported in the clinical studies, there were findings suggestive of opportunistic infections in the non-clinical studies [see Section 5.R.3]. In addition, there have been reports of infections caused by encapsulated bacteria other than *Neisseria meningitidis* in the clinical studies of eculizumab and other data (Review Report of "Soliris for Intravenous Infusion 300 mg," dated November 24, 2017, and Review Report of "Ultomiris for Intravenous Infusion 300 mg and other dosage," dated July 14, 2022). Given these findings, infections caused by encapsulated bacteria other than *Neisseria meningitidis* potentially occur. Therefore, increased vigilance for infections caused by encapsulated bacteria in addition to *Neisseria meningitidis* is required in patients being treated with zilucoplan.

Because currently available data from the clinical studies include only a small number of patients with a limited duration of treatment, the applicant should collect post-marketing data on the incidence of encapsulated bacterial infections including meningococcal infections associated with the use of zilucoplan to continue to evaluate the effectiveness of the safety measures, and should take additional safety measures as necessary.

7.R.3.2.2 Other infections

PMDA asked the applicant to explain the incidence of infections caused by pathogens other than encapsulated bacteria tin patients being treated with zilucoplan:

The applicant's explanation:
Table 59 shows the incidence of infections caused by pathogens other than encapsulated bacteria. Analyses of data from Studies MG0009 and MG0010 and gMG double-blind pooled data showed that the incidence of such infections was higher in the zilucoplan group than in the placebo group, while the incidence of serious adverse events was similar between the groups.

Whether the infections reported can be classified as opportunistic infections was studied. In the gMG double-blind pooled data, infections classified as opportunistic infections [30)] occurred in 11 subjects in the zilucoplan group (COVID-19 [3 subjects], COVID-19 pneumonia [1 subject], escherichia urinary tract infection [1 subject], herpes zoster [1 subject], influenza [1 subject], sepsis [1 subject], bacterial test positive [1 subject], systemic inflammatory response syndrome [1 subject], oesophageal candidiasis [1 subject], oral

30) Adverse events coded to the "narrow" and "broad" definitions of Standardized Medical Dictionary for Regulatory Activities Japanese version (MedDRA) Query (SMQ) "opportunistic infections."

candidiasis [1 subject], vulval candida [1 subject]) and in 6 subjects in the placebo group (COVID-19 [4 subjects], COVID-19 pneumonia [2 subjects], herpes simplex meningoencephalitis [1 subject], and vulvovaginal candidiasis [1 subject]). All of the subjects were found to have risk factors such as immunosuppressant therapy, denture use, and intravenous catheter insertion.

The results of a subgroup analysis by concomitant drug in Study MG0010 showed no marked difference in the incidence of infections regardless of the use of concomitant corticosteroids or immunosuppressants. The incidence of infections in subjects who received corticosteroids was 23.7% (14 of 59 subjects) in the zilucoplan group and 17.6% (9 of 51 subjects) in the placebo group; that in subjects who did not receive corticosteroids was 33.3% (9 of 27 subjects) in the zilucoplan group and 18.9% (7 of 37 subjects) in the placebo group; that in subjects who received immunosuppressants was 19.5% (8 of 41 subjects) in the zilucoplan group and 14.6% (7 of 48 subjects) in the placebo group; and that in subjects who did not receive immunosuppressants was 33.3% (15 of 45 subjects) in the zilucoplan group and 22.5% (9 of 40 subjects) in the placebo group.

Published literature has reported that deficiency of complement components (C1 through C4) is associated with increased susceptibility to many infections (*FEBS Letters.* 2020;594:2670-94, *Mol Immunol.* 2011;48:1643-55); however, zilucoplan does not inhibit early complement components (C1 through C4). In addition, in the clinical studies of eculizumab, another C5 inhibitor, the incidence of infections in the eculizumab group was comparable to that in the placebo group irrespective of use/non-use or the type of concomitant immunosuppressants (*72nd Annual Meeting of the American Academy of Neurology.* AAN 2020;94, *Ann Neurol.* 2021;89:1088-98). Currently, therefore, there is no clear evidence supporting that C5 inhibitors including zilucoplan increase the incidence of infections, with the exception of infections caused by encapsulated bacteria.

On the basis of the above findings, there are no data that clearly suggest that there is an increased risk of infections associated with the use of zilucoplan, with the exception of infections caused by encapsulated bacteria.

Table 59. Summary of common infection-related adverse events (excluding those related to infections caused by encapsulated bacteria) (safety analysis set)

	MG0009			MG0010		MG0011	gMG double-blind pooled data	
	Placebo	Zilucoplan 0.1 mg/kg	Zilucoplan 0.3 mg/kg	Placebo	Zilucoplan 0.3 mg/kg	Overall	Placebo	Zilucoplan
N	15	15	14	88	86	200	103	115
Any adverse event	3 (20.0)	3 (20.0)	6 (42.9)	16 (18.2)	23 (26.7)	130 (65.0)	19 (18.4)	33 (28.7)
Serious adverse events	0	0	2 (14.3)	4 (4.5)	4 (4.7)	23 (11.5)	4 (3.9)	6 (5.2)
Adverse events leading to treatment discontinuation (including death)	0	0	0	0	1 (1.2)	2 (1.0)	0	1 (0.9)
Adverse events occurring in ≥5% of subjects in any group								
COVID-19	0	0	0	4 (4.5)	3 (3.5)	49 (24.5)	4 (3.9)	3 (2.6)
Nasopharyngitis	0	1 (6.7)	0	3 (3.4)	5 (5.8)	30 (15.0)	3 (2.9)	6 (5.2)
Upper respiratory tract infection	0	0	0	3 (3.4)	2 (2.3)	23 (11.5)	3 (2.9)	3 (2.6)
Urinary tract infection	0	1 (6.7)	0	4 (4.5)	7 (8.1)	23 (11.5)	4 (3.9)	8 (7.0)
Sinusitis	0	0	0	0	4 (4.7)	10 (5.0)	0	4 (3.5)
Bronchitis	0	1 (6.7)	1 (7.1)	0	0	9 (4.5)	0	2 (1.7)
Cellulitis	0	0	1 (7.1)	0	1 (1.2)	9 (4.5)	0	2 (1.7)
Pneumonia	1 (6.7)	0	0	0	1 (1.2)	6 (3.0)	1 (1.0)	1 (0.9)
Herpes zoster	0	0	1 (7.1)	0	0	4 (2.0)	0	1 (0.9)
Viral infection	0	0	1 (7.1)	0	0	4 (2.0)	0	1 (0.9)
Conjunctivitis	0	0	0	0	0	3 (1.5)	0	0
Diverticulitis	0	0	1 (7.1)	1 (1.1)	0	3 (1.5)	1 (1.0)	1 (0.9)
Localised infection	0	0	1 (7.1)	0	0	2 (1.0)	0	1 (0.9)
Pharyngitis	1 (6.7)	0	0	0	0	2 (1.0)	1 (1.0)	0
Abdominal abscess	0	0	1 (7.1)	0	0	1 (0.5)	0	1 (0.9)
Vaginal infection	1 (6.7)	0	0	0	0	1 (0.5)	1 (1.0)	0
Viral upper respiratory tract infection	1 (6.7)	0	1 (7.1)	0	0	1 (0.5)	1 (1.0)	1 (0.9)
Escherichia urinary tract infection	0	0	1 (7.1)	0	0	0	0	1 (0.9)

n (%)

PMDA's view:

The applicant explained that no data have clearly suggested that there is an increased risk of infections associated with the use of zilucoplan, with the exception of infections caused by encapsulated bacteria. However, there were findings suggestive of opportunistic infections in the non-clinical studies [see Section 5.R.3]. In the clinical studies, the incidence of infections including opportunistic infections (excluding infections caused by encapsulated bacteria) was higher in the zilucoplan group than in the placebo group, and serious adverse events and adverse events leading to treatment discontinuation were also reported in the zilucoplan group.

Based on the above, increased vigilance is required not only for encapsulated bacterial infections, but also infections caused by other pathogens in patients being treated with zilucoplan.

7.R.3.3 Pancreatic adverse events

In the non-clinical studies, pancreatic findings (e.g., acinar degeneration, pancreatic duct hyperplasia, elevated lipase, and elevated amylase) were reported [see Section 5.2]. PMDA asked the applicant to explain the incidence of pancreatic adverse events[31)] associated with zilucoplan.

31) Adverse events coded to MedDRA high level group term (HLGT) "exocrine pancreas conditions" or PTs "amylase increased," "lipase increased," "pancreatic carcinoma," or "pancreas infection."

The applicant's explanation:

Table 60 shows the incidence of pancreatic adverse events in the clinical studies. Serious adverse events occurred only in the zilucoplan group (pancreas infection [2 subjects], lipase increased [1 subject], pancreatitis [1 subject], pancreatitis acute [1 subject], pancreatic cyst [1 subject], and pancreatic mass [1 subject]). Amylase and lipase elevations were generally transient and resolved with continued treatment with zilucoplan. Only 1 adverse event (lipase increased) led to treatment discontinuation in 1 subject in Study MG0011, and its causal relationship to zilucoplan could not be ruled out. Pancreatitis (including pancreatitis acute) was reported as an adverse event in 3 subjects in the clinical studies, 2 [32] of whom experienced pancreatitis after endoscopic retrograde cholangiopancreatography (ERCP), and the events were considered unrelated to zilucoplan. Pancreatitis in the remaining 1 subject,[33] for which a causal relationship to zilucoplan could not be ruled out, was mild in severity and resolved without discontinuing treatment with zilucoplan. This subject experienced elevated amylase and lipase levels along with a diagnosis of pancreatitis, which however did not meet the criteria for acute pancreatitis according to the American College of Gastroenterology. Other pancreatic adverse events reported were pancreatic cyst (3 subjects), pancreas infection (2 subjects), pancreatic carcinoma[34] (1 subject), and pancreatic mass (1 subject). All of these events were considered unrelated to the study drug. Treatment with zilucoplan was continued in the subjects with pancreatic adverse events, except for the subject who died due to pancreatic carcinoma. In the subject[35] who had a pancreatic mass, marked atypical pancreatic ductal cells were observed, which was consistent with the observation of adenocarcinoma; however, the diagnosis was not confirmed due to an insufficient number of cells in the specimen.

Amylase and lipase levels were measured periodically in the clinical studies, and the changes over time of the pancreatic enzymes were examined. While the time to peak of amylase or lipase levels during the study period varied subject to subject, amylase reached its peak at Week 8 and lipase at Week 12 in the majority of subjects. Most of subjects who experienced elevated amylase or lipase were asymptomatic, with no symptoms such as abdominal pain. None of the subjects met the diagnostic criteria for acute pancreatitis according to the American College of Gastroenterology criteria. Furthermore, serum amylase increased or lipase increased corresponding to the Common Terminology Criteria for Adverse Events (CTCAE) Grade 3/4 occurred in 16 subjects in the zilucoplan group and 6 subjects in the placebo group in the gMG double-blind pooled data. Although these events occurred more frequently in the zilucoplan group than in the placebo group, the use of concomitant corticosteroids and complications of diabetes mellitus or other diseases could have resulted in amylase or lipase elevation in these subjects.

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32) One of the subjects (Study MG0009), a male aged in his 50s, had cholecystitis acute at the start of treatment with zilucoplan. At 122 days after the initial dose of zilucoplan (Day 122), the subject underwent a re-ERCP with biliary stent placement for post-cholecystectomy bile leak management, and biliary stent exchange at Day 130. At Day 144, the subject developed pancreatitis acute (amylase and lipase elevations occurred 24 hours after re-ERCP). The event was classified as a serious adverse event, but its causal relationship to zilucoplan was ruled out. The other subject (Study MG0011), a male in his 60s, developed pancreatitis concurrently with the onset of cholangitis 24 hours after an ERCP for gallstones at 2 years of treatment with zilucoplan. The event was classified as a serious adverse event, but its causal relationship to zilucoplan was ruled out.

33) This subject (Study MG0011), a male in his 50s, had elevated amylase and lipase levels at Day 77 and was diagnosed as having pancreatitis. The event was classified as a non-serious adverse event, and its causal relationship to zilucoplan could not be ruled out.

34) This subject, a male in his 70s, had pancreatic carcinoma in the extension portion of Study MG0009. The subject did not participate in Study MG0011, and died 71 days after the completion of treatment with zilucoplan. Therefore, it is not included in Table 60 as an adverse event.

35) The subject, a white male in his 60s, developed transaminases increased, classified as a serious adverse event, at Day 91, and pancreatic mass (Grade 3) at Day 94. Transaminases increased was thought to be attributable to prostate cancer metastatic by the principal investigator. The subject showed marked atypical pancreatic ductal cells, which was consistent with the observation of adenocarcinoma; however, the diagnosis was not confirmed due to an insufficient number of cells in the specimen.

In the clinical studies, the proportion of subjects who experienced amylase or lipase elevation is higher in the zilucoplan group than in the placebo group; therefore, increased vigilance is required for amylase or lipase elevation in patient being treated with zilucoplan; however, elevation of amylase or lipase levels is unlikely to cause clinically relevant problems in patients during treatment with zilucoplan.

Table 60. Summary of pancreatic adverse events (safety analysis set)

	MG0009			MG0010		MG0011	gMG double-blind pooled data	
	Placebo	Zilucoplan 0.1 mg/kg	Zilucoplan 0.3 mg/kg	Placebo	Zilucoplan 0.3 mg/kg	Overall	Placebo	Zilucoplan
N	15	15	14	88	86	200	103	115
Any adverse event	3 (20.0)	0	2 (14.3)	2 (2.3)	7 (8.1)	20 (10.0)	5 (4.9)	9 (7.8)
Serious adverse events	0	0	0	0	1 (1.2)	4 (2.0)	0	1 (0.9)
Adverse events leading to treatment discontinuation	0	0	0	0	0	1 (0.5)	0	0
Adverse events								
Lipase increased	2 (13.3)	0	1 (7.1)	1 (1.1)	7 (8.1)	13 (6.5)	3 (2.9)	7 (6.1)
Amylase increased	1 (6.7)	0	2 (14.3)	2 (2.3)	5 (5.8)	8 (4.0)	3 (2.9)	7 (6.1)
Pancreatic cyst	0	0	0	0	0	3 (1.5)	0	0
Pancreatitis	0	0	0	0	0	2 (1.0)	0	0
Pancreas infection	0	0	0	0	0	2 (1.0)	0	0
Pancreatitis acute	0	0	0	0	0	1 (0.5)	0	0
Pancreatic mass	0	0	0	0	0	1 (0.5)	0	0
Pancreatic steatosis	0	0	0	0	0	1 (0.5)	0	0

n (%)

PMDA's view:

Many of the pancreatic adverse events reported during the clinical studies, such as elevated blood amylase and lipase levels, were mild to moderate in severity, and the subjects with such events were able to continue zilucoplan treatment. However, the proportion of subjects who experienced elevation of blood amylase or lipase in the clinical studies was higher in the zilucoplan group than in the placebo group. In addition, the proportion of subjects who had CTCAE Grade 3/4 serum amylase increased or lipase increased was higher in the zilucoplan group than in the placebo group. An increase in lipase leading to treatment discontinuation for which a causal relationship to the study drug could not be ruled out occurred only in the zilucoplan group.

Based on the above findings, elevation of blood amylase or lipase may occur in association with the use of zilucoplan and there may be a risk of pancreatitis. Blood pancreatic enzyme levels should be monitored in patients being treated with zilucoplan on a regular basis to ascertain if they have increased.

7.R.3.4 Hepatic dysfunction-related adverse events

Since hepatic findings in the non-clinical studies include jaundice, hepatic fibrosis, hyperplasia of the bile duct epithelium, pericholangitis, and elevated hepatic enzymes [see Section 5.2], PMDA asked the applicant to explain the incidence of hepatic dysfunction-related adverse events.[36)]

36) Adverse events coded to MedDRA SMQ "drug related hepatic disorders–comprehensive search" excluding those coded to "liver neoplasms benign (incl cysts and polyps)" and "liver neoplasms, malignant and unspecified."

The applicant's explanation:

Table 61 shows the incidence of hepatic dysfunction-related adverse events in the clinical studies. A serious adverse event (transaminases increased) [35)] occurred in 1 subject. A causal relationship to zilucoplan was ruled out and the adverse event did not lead to treatment discontinuation. No adverse events met the Hy's law criteria. There were no abnormal laboratory test results. Although an adverse event (hepatic enzyme increased) led to discontinuation of the study drug in 1 subject, the event was classified as non-serious. The subject had had elevated liver function test values[37)] before the start of treatment with zilucoplan, and a causal relationship to the study drug was ruled out. The outcome was reported as "not resolved."

The change over time of liver function test values measured periodically in the clinical studies was examined. In the gMG double-blind pooled data, there was 1 subject (zilucoplan group) who had an elevation in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) to a level >3 × upper limit of normal (ULN). The subject had AST and ALT levels >5 × ULN. In the zilucoplan 0.3 mg/kg group in the gMG overall pooled data, 3 of 212 subjects (1.4%) had AST elevation >3 × ULN and 2 of 212 subjects (0.9%) had ALT elevation >3 × ULN, while 2 of 212 subjects (0.9%) had AST elevation >5 × ULN and 1 of 212 subjects (0.5%) had ALT elevation >5 × ULN.

As described above, the incidence of hepatic dysfunction-related adverse events was low in the clinical studies, with no difference between the zilucoplan and placebo groups. Therefore, the data do not suggest that there is a risk of hepatic dysfunction associated with the use of zilucoplan.

Table 61. Summary of hepatic dysfunction-related adverse events (safety analysis set)

	MG0009			MG0010		MG0011	gMG double-blind pooled data	
	Placebo	Zilucoplan 0.1 mg/kg	Zilucoplan 0.3 mg/kg	Placebo	Zilucoplan 0.3 mg/kg	Overall	Placebo	Zilucoplan
N	15	15	14	88	86	200	103	115
Any adverse event	0	0	0	1 (1.1)	3 (3.5)	12 (6.0)	1 (1.0)	2 (1.7)
Serious adverse events	0	0	0	0	0	1 (0.5)	0	0
Adverse events leading to treatment discontinuation	0	0	0	0	1 (1.2)	0	0	1 (0.9)
Adverse events								
ALT increased	0	0	0	0	1 (1.2)	5 (2.5)	0	0
AST increased	0	0	0	0	0	3 (1.5)	0	0
Hepatic steatosis	0	0	0	1 (1.1)	0	3 (1.5)	1 (1.0)	0
γ-GTP increased	0	0	0	0	0	2 (1.0)	0	0
Hypofibrinogenaemia	0	0	0	0	0	1 (0.5)	0	0
Liver function test increased	0	0	0	0	0	1 (0.5)	0	0
Transaminases increased	0	0	0	0	0	1 (0.5)	0	0
Hepatic enzyme increased	0	0	0	0	1 (1.2)	0	0	1 (0.9)
Hepatic pain	0	0	0	0	1 (1.2)	0	0	1 (0.9)

n (%)

PMDA's view:

The incidence of hepatic dysfunction-related adverse events and the proportion of subjects who had elevated liver function test values in the zilucoplan group in the clinical studies did not show clear increasing trends

37) At baseline: AST = 39 U/L (normal range, 8-40 U/L), ALT = 93 U/L (normal range, 5-48 U/L), ALP = 177 U/L (normal range, 40-129 U/L), GGT = 286 U/L (normal range, 10-50 U/L).

compared to placebo. However, given that elevation of AST or ALT, which is possibly related to zilucoplan, occurred only in the zilucoplan group, hepatic dysfunction may occur in patients during treatment with zilucoplan.

7.R.3.5 Adverse events related to hypersensitivity reactions or injection site reactions

PMDA asked the applicant to explain the incidence of adverse events related to hypersensitivity reactions[38)] or injection site reactions[39)] in subjects treated with zilucoplan.

The applicant's explanation:

Table 62 shows the incidence of adverse events related to hypersensitivity reactions in the clinical studies. In the gMG double-blind pooled data, the incidence of adverse events related to hypersensitivity reactions was 11.3% (13 of 115 subjects) in the zilucoplan group, which was higher than that in the placebo group, 8.7% (9 of 103 subjects). The reported events were mild to moderate in severity. A serious adverse event, angioedema, occurred in 1 subject[40)] in the zilucoplan group of Study MG0010, and the event was considered related to zilucoplan. This subject developed acute urticaria (moderate) and angioedema (mild) about 20 days after the start of zilucoplan treatment. The events resolved after interruption of zilucoplan treatment and did not recur after resumption of zilucoplan. Although the incidence of adverse events related to hypersensitivity reactions tended to be higher in the zilucoplan group than in the placebo group, the reported events were all mild to moderate in severity, and therefore hypersensitivity reactions are unlikely to cause a significant problem in clinical settings.

38) Adverse events coded to MedDRA SMQ "hypersensitivity."
39) Adverse events coded to MedDRA high level terms (HLTs) "injection site reactions" and "administration site reactions NEC."
40) The subject, a female in her 20s, developed mild acute urticaria 21 days after the start of study drug (Day 21). On Day 23, the severity of urticaria worsened from mild to moderate and mild angioedema developed. The subject was taken to the hospital by ambulance. The subject started to receive oral cetirizine for the treatment of urticaria on the same day. Angioedema resolved on Day 24 and the subject was discharged from the hospital.

Table 62. Summary of adverse events related to hypersensitivity reactions (safety analysis set)

	MG0009			MG0010		MG0011	gMG double-blind pooled data	
	Placebo	Zilucoplan 0.1 mg/kg	Zilucoplan 0.3 mg/kg	Placebo	Zilucoplan 0.3 mg/kg	Overall	Placebo	Zilucoplan
N	15	15	14	88	86	200	103	115
Any adverse event	1 (6.7)	2 (13.3)	3 (21.4)	8 (9.1)	8 (9.3)	33 (16.5)	9 (8.7)	13 (11.3)
Serious adverse events	0	0	0	0	1 (1.2)	0	0	1 (0.9)
Adverse events leading to treatment discontinuation	0	0	0	0	0	1 (0.5)	0	0
Adverse events								
Rash	0	1 (6.7)	1 (7.1)	5 (5.7)	3 (3.5)	15 (7.5)	5 (4.9)	5 (4.3)
Dermatitis contact	1 (6.7)	1 (6.7)	2 (14.3)	0	1 (1.2)	7 (3.5)	1 (1.0)	4 (3.5)
Eczema	0	0	0	0	0	5 (2.5)	0	0
Injection site rash	0	0	0	2 (2.3)	0	4 (2.0)	2 (1.9)	0
Dermatitis allergic	0	0	0	0	0	2 (1.0)	0	0
Urticaria	0	0	0	0	3 (3.5)	1 (0.5)	0	3 (2.6)
Rash pruritic	0	0	0	0	1 (1.2)	1 (0.5)	0	1 (0.9)
Eye swelling	0	0	0	0	0	1 (0.5)	0	0
Periorbital swelling	0	0	0	0	0	1 (0.5)	0	0
Swollen tongue	0	0	0	0	0	1 (0.5)	0	0
Vaccination site rash	0	0	0	0	0	1 (0.5)	0	0
Dermatitis	0	0	0	0	0	1 (0.5)	0	0
Angioedema	0	0	0	0	1 (1.2)	0	0	1 (0.9)
Drug eruption	0	0	0	0	1 (1.2)	0	0	1 (0.9)
Swelling face	0	0	1 (7.1)	0	0	0	0	1 (0.9)
Rhinitis allergic	0	0	0	1 (1.1)	0	0	1 (1.0)	0

n (%)

Table 63 and Table 64 show the incidence of adverse events related to injection site reactions in the clinical studies. The incidence of injection site reactions was higher in the zilucoplan group than in the placebo group. Injection site reactions occurred more frequently within 29 days after the start of study drug than at 30 days and thereafter, during which the incidence tended to decrease with an increase in the duration of treatment. The reported adverse events were all mild to moderate in severity, and none of the events were classified as serious adverse events. Adverse events led to treatment discontinuation in 2 subjects in the zilucoplan group (injection site bruising/injection site rash [1 subject] and injection site pain [1 subject]).

Based on the above findings, although injection site reactions may occur in patients being treated with zilucoplan, given the severity of the events and other aspects, there are no concerns that injection site reactions could cause significant problems in clinical settings.

Table 63. Incidence of common adverse events related to injection site reactions by time to onset in the gMG double-blind pooled data (safety analysis set)

Evaluation timepoint	Placebo			Zilucoplan		
	Overall study period	≤29 days	≥30 days	Overall study period	≤29 days	≥30 days
N	103	103	101	115	115	113
Adverse events related to injection site reactions	16 (15.5)	15 (14.6)	1 (1.0)	29 (25.2)	23 (20.0)	10 (8.8)
Injection site bruising	10 (9.7)	9 (8.7)	1 (1.0)	16 (13.9)	10 (8.7)	6 (5.3)
Injection site discomfort	0	0	0	1 (0.9)	1 (0.9)	0
Injection site haematoma	0	0	0	2 (1.7)	2 (1.7)	0
Injection site haemorrhage	0	0	0	2 (1.7)	1 (0.9)	1 (0.9)
Injection site mass	0	0	0	1 (0.9)	0	1 (0.9)
Injection site nodule	0	0	0	1 (0.9)	0	1 (0.9)
Injection site pain	4 (3.9)	4 (3.9)	0	8 (7.0)	8 (7.0)	0
Injection site reaction	0	0	0	1 (0.9)	0	1 (0.9)
Injection site scab	0	0	0	3 (2.6)	3 (2.6)	1 (0.9)
Injection site rash	2 (1.9)	2 (1.9)	0	0	0	0

n (%)

Table 64. Incidence of common adverse events related to injection site reactions by time to onset in the gMG overall pooled data (safety analysis set)

Evaluation timepoint	Overall study period	≤29 days	30-90 days	91-181 days	182-364 days	≥365 days
N	213	213	209	203	192	135
Adverse events related to injection site reactions	63 (29.6)	32 (15.0)	19 (9.1)	16 (7.9)	10 (5.2)	17 (12.6)
Injection site bruising	33 (15.5)	13 (6.1)	10 (4.8)	8 (3.9)	4 (2.1)	5 (3.7)
Injection site discomfort	1 (0.5)	1 (0.5)	0	0	1 (0.5)	1 (0.7)
Injection site erythema	2 (0.9)	1 (0.5)	0	1 (0.5)	0	0
Injection site haematoma	2 (0.9)	2 (0.9)	0	0	0	0
Injection site haemorrhage	3 (1.4)	1 (0.5)	2 (1.0)	0	0	0
Injection site irritation	1 (0.5)	0	0	0	0	1 (0.7)
Injection site mass	3 (1.4)	0	1 (0.5)	1 (0.5)	0	1 (0.7)
Injection site nodule	8 (3.8)	0	1 (0.5)	1 (0.5)	0	6 (4.4)
Injection site pain	18 (8.5)	12 (5.6)	2 (1.0)	2 (1.0)	2 (1.0)	1 (0.7)
Injection site pruritus	3 (1.4)	1 (0.5)	1 (0.5)	1 (0.5)	0	0
Injection site rash	4 (1.9)	0	0	2 (1.0)	2 (1.0)	0
Injection site reaction	7 (3.3)	1 (0.5)	3 (1.4)	2 (1.0)	2 (1.0)	0
Injection site scab	3 (1.4)	3 (1.4)	1 (0.5)	0	0	0
Injection site swelling	2 (0.9)	0	0	1 (0.5)	0	1 (0.7)
Injection site vesicles	1 (0.5)	0	0	0	0	1 (0.7)

n (%)

PMDA's view:

Adverse events related to hypersensitivity reactions reported in subjects on zilucoplan in the clinical studies were all mild to moderate in severity, and the subjects were able to continue receiving zilucoplan. However, in the gMG double-blind pooled data, the incidence of adverse events related to hypersensitivity reactions was higher in the zilucoplan group than in the placebo group, and there was a report of a serious adverse event, angioedema, for which a causal relationship to zilucoplan could not be ruled out. Therefore, physicians should be advised that angioedema and other serious hypersensitivity reactions may occur in patients during treatment with zilucoplan.

In the gMG double-blind pooled data, the incidence of adverse events related to injection site reactions was higher in the zilucoplan group than in the placebo group. Although injection site reactions may be caused by injection of zilucoplan, the adverse events related to injection site reactions in subjects treated with zilucoplan in the clinical studies were all mild to moderate in severity, and the subjects were able to continue treatment with zilucoplan. Therefore, at present, injection site reactions are unlikely to cause a significant problem in clinical settings.

7.R.3.6 Increase in eosinophil count

Since complement C5a is involved in induction of eosinophil activation and extravasation (*Int Arch Allergy Immunol.* 1995;107:345, *Allergy.* 1995;50:34-47), the applicant provided the following explanation about the incidence of adverse events related to increased eosinophil count[41)] in the clinical studies and the impact of C5 inhibition by zilucoplan on eosinophils.

Eosinophil count was measured on a regular basis during the clinical studies. In the gMG double-blind pooled data, 21 subjects had elevated eosinophil count after initiation of study drug, with a higher incidence in the zilucoplan group (19 of 127 subjects; 15.0%) than in the placebo group (2 of 118 subjects; 1.7%). All subjects

41) Adverse events coded to MedDRA PTs "eosinophilia," "eosinophil count increased," or "eosinophil percentage increased."

had normal eosinophil count at baseline except for 1 subject in the placebo group who had a high baseline eosinophil count. While time to onset of elevation of eosinophil count varied subject to subject, the highest increase in eosinophil count occurred at 8 weeks after the start of study drug in most subjects. In the gMG double-blind pooled data, of the 21 subjects who had increased eosinophil count after receiving the study drug, 6 subjects had an eosinophil count $\geq 1.5 \times 10^9$/L, defined as eosinophilia. All of these subjects were in the zilucoplan group, but none of them presented with pyrexia, infection parasitic, or other clinically relevant findings. Eosinophil count returned to normal in 5 of the 6 subjects without interruption of zilucoplan.

Table 65 shows the incidence of adverse events related to increased eosinophil count in the clinical studies. In the gMG double-blind pooled data and Study MG0011, a total of 2 subjects had adverse events related to increased eosinophil count. Both events were mild in severity, and neither subject had pyrexia or clinically relevant organ dysfunction, eosinophilic lesions, hypersensitivity/allergic reaction after initiation of zilucoplan treatment, or other events that may be related to eosinophilia.

The cases of increased eosinophil count reported in the clinical studies were generally transient and asymptomatic. Most of the events resolved without interruption of zilucoplan, and there were no clinically relevant findings related to increased eosinophil count. Therefore, no concerns have been raised regarding adverse events related to increased eosinophil count in patients during treatment with zilucoplan in clinical settings.

Table 65. Summary of adverse events related to increased eosinophil count (safety analysis set)

	MG0009			MG0010		MG0011	gMG double-blind pooled data	
	Placebo	Zilucoplan 0.1 mg/kg	Zilucoplan 0.3 mg/kg	Placebo	Zilucoplan 0.3 mg/kg	Overall	Placebo	Zilucoplan
N	15	15	14	88	86	200	103	115
Any adverse event	0	0	0	0	1 (1.2)	1 (0.5)	0	1 (0.9)
Serious adverse events	0	0	0	0	0	0	0	0
Adverse events leading to treatment discontinuation (including death)	0	0	0	0	0	0	0	0
Adverse events								
Eosinophilia	0	0	0	0	1 (1.2)	0	0	1 (0.9)
Eosinophil count increased	0	0	0	0	0	1 (0.5)	0	0

n (%)

PMDA's view:

Since the proportion of subjects who had increased eosinophil count was higher in the zilucoplan group than in the placebo group in the clinical studies, increased eosinophil count may occur in patients receiving treatment with zilucoplan in clinical settings. However, the cases of increased eosinophil count reported in the clinical studies were generally transient and asymptomatic, and resolved without interruption of zilucoplan in most of subjects. In addition, no clinically relevant findings related to increased eosinophil count were noted in subjects who had eosinophil elevation.

Based on the currently available data, PMDA concluded that increased eosinophil count associated with the use of zilucoplan is unlikely to cause a significant problem in patients being treated with zilucoplan in clinical settings.

7.R.3.7 Malignancy-related adverse events

It is known that in general, immunosuppression can be a risk factor for malignancy in humans (*Regul Toxicol Pharmacol.* 2016;75:72-80, *Int J Toxicol.* 2010;29:435-66), and zilucoplan is an immunosuppressant with a mechanism of action based on C5 inhibition. For this reason, PMDA asked the applicant to explain the incidence of malignancy-related adverse events[42)] associated with zilucoplan.

The applicant's explanation:

Table 66 shows the incidence of malignancy-related adverse events in the clinical studies. In the gMG double-blind pooled data, the incidence of malignancy-related adverse events was slightly higher in the zilucoplan group than in the placebo group. There were no trends specific to the type of malignancies identified in either pooled data analysis.

Data on malignancy (excluding malignant melanoma) from the Surveillance Epidemiology and End Results Program of the National Cancer Institute were used to calculate the age- and sex-adjusted standardized incidence ratio (SIR) for malignancy in the pooled zilucoplan group.[43)] The SIR (with the 95% CI) was 1.86 [0.67, 3.64], which did not tend to be clearly higher in the pooled zilucoplan group than in the general population. In general, immune-mediated diseases including gMG may increase the risk of malignancy. According to studies conducted outside Japan, any immune-mediated diseases were associated with a slight increase in total malignancy risk (hazard ratio with 95% CI, 1.08 [1.04, 1.12]) (*JAMAOncol.* 2022;8:209-19) and the risk for non-Hodgkin lymphoma was higher in patients with MG (SIR with 95% CI, 2.2 [1.4, 3.3]) (*Ann Oncol.* 2014;25:2025-30). In the clinical studies of two other inhibitors, eculizumab and ravulizumab, no increased risk of malignancy has been reported so far. There have been no findings suggestive of increased malignancy risk in patients with congenital C5 deficiency (e.g., *Mol Immunol.* 2015;64:170-6, *J Clin Immunol.* 2013;33:871-5).

Therefore, the currently available information indicates that there is no concern about an increased incidence of malignancy due to zilucoplan treatment.

42) Adverse events coded to MedDRA SMQ "malignant or unspecified tumours" or "malignant tumors."
43) A pooled analysis population comprising data from Study MG0009 (double-blind and open-label data), Study MG0010 (double-blind data), Study MG0011 (open-label data), and Study IMNM01 (double-blind and open-label data).

Table 66. Summary of malignancy-related adverse events (safety analysis set)

	MG0009			MG0010		MG0011	gMG double-blind pooled data	
	Placebo	Zilucoplan 0.1 mg/kg	Zilucoplan 0.3 mg/kg	Placebo	Zilucoplan 0.3 mg/kg	Overall	Placebo	Zilucoplan
N	15	15	14	88	86	200	103	115
Any adverse event	0	0	2 (14.3)	1 (1.1)	1 (1.2)	7 (3.5)	0	3 (2.6)
Serious adverse events	0	0	0	1 (1.1)	1 (1.2)	3 (1.5)	0	1 (0.9)
Adverse events leading to treatment discontinuation	0	0	0	0	0	0	0	0
Adverse events								
Bone neoplasm	0	0	0	0	0	1 (0.5)	0	0
Metastatic neoplasm	0	0	0	0	0	1 (0.5)	0	0
Abdominal neoplasm	0	0	0	0	0	1 (0.5)	0	0
Malignant melanoma	0	0	0	0	0	1 (0.5)	0	0
Metastatic malignant melanoma	0	0	0	0	0	1 (0.5)	0	0
Basal cell carcinoma	0	0	1 (7.1)	0	1 (1.2)	2 (1.0)	0	2 (1.7)
Squamous cell carcinoma	0	0	2 (14.3)	0	0	0	0	2 (1.7)
Metastases to meninges	0	0	0	1 (1.1)	0	0	0	0

n (%)

PMDA's view:

Zilucoplan is an immunosuppressant with a mechanism of action based on C5 inhibition, and malignancy-related adverse events were reported in patients treated with zilucoplan in the clinical studies. However, as presented by the applicant, patients with immune-mediated diseases such as gMG are at an increased risk of malignancy, while no increased risk of malignancy associated with C5 inhibitors has been reported. Taken together, currently, the data submitted by the applicant raise no clear concerns about an increased incidence of malignancy; however, because of limitations in the number of subjects treated, duration of treatment, and other factors in the clinical studies from which the currently available data were obtained, the applicant should continue to collect post-marketing data on the risk of malignancy resulting from immunosuppression caused by inhibition of C5 by zilucoplan or other C5 inhibitors, and take appropriate action promptly as necessary.

7.R.3.8 Adverse events associated with skin/oral mucosal ulceration

In the non-clinical studies, skin findings (e.g., erosion, ulcer) and oral findings (ulcer, erythema in the buccal mucosa) were reported [see Section 5.2]. PMDA asked the applicant to explain the incidence of adverse events related to skin/oral mucosal ulceration.[44)]

The applicant's explanation:

Table 67 shows the incidence of adverse events related to skin/oral mucosal ulceration in the clinical studies. A serious adverse event (aphthous ulcer) occurred in 1 subject. The event was considered related to zilucoplan, and treatment with zilucoplan was discontinued. Other adverse events leading to treatment discontinuation occurred in 2 subjects in Study MG0010 (mouth ulceration [1 subject] and aphthous ulcer [1 subject]) and 1 subject in Study MG0011 (stomatitis). A causal relationship to the study drug was ruled out for all the events.

Based on the above findings, adverse events related to skin/oral mucosal ulceration are unlikely to cause a clinically relevant problem in association with the use of zilucoplan in clinical settings because most of the adverse events related to skin/oral mucosal ulceration reported in the clinical studies were mild in severity and

44) Adverse events classified as MedDRA HLT "skin and subcutaneous tissue ulcerations" or "stomatitis and ulceration."

subjects were able to continue treatment with zilucoplan, even though there were reports of adverse events leading to treatment discontinuation and a serious adverse event.

Table 67. Summary of adverse events related to skin/oral mucosal ulceration (safety analysis set)

	MG0009			MG0010		MG0011	gMG double-blind pooled data	
	Placebo	Zilucoplan 0.1 mg/kg	Zilucoplan 0.3 mg/kg	Placebo	Zilucoplan 0.3 mg/kg	Overall	Placebo	Zilucoplan
N	15	15	14	88	86	200	103	115
Any adverse event	1 (6.7)	0	0	1 (1.1)	4 (4.7)	5 (2.5)	2 (1.9)	5 (4.3)
Serious adverse events	0	0	0	0	1 (1.2)	0	0	1 (0.9)
Adverse events leading to treatment discontinuation	0	0	0	0	2 (2.3)	1 (0.5)	0	2 (1.7)
Adverse events								
Aphthous ulcer	0	0	0	0	2 (2.3)	1 (0.5)	0	3 (2.6)
Lip ulceration	0	0	0	1 (1.1)	0	1 (0.5)	1 (1.0)	0
Mouth ulceration	1 (6.7)	0	0	0	2 (2.3)	0	1 (1.0)	2 (1.7)
Skin ulcer	0	0	0	0	0	1 (0.5)	0	0
Stomatitis	0	0	0	0	0	2 (1.0)	0	0

n (%)

PMDA's view:

In the gMG double-blind pooled data, adverse events related to skin/oral mucosal ulceration occurred more frequently in the zilucoplan group than in the placebo group, and a causal relationship to zilucoplan could not be ruled out for some events. Therefore, adverse events related to skin/oral mucosal ulceration may occur in patients receiving zilucoplan in clinical settings. However, most of the events reported in the clinical studies were mild in severity, and subjects were able to continue treatment with zilucoplan. PMDA concluded that adverse events related to skin/oral mucosal ulceration are unlikely to cause a significant problem in association with the use of zilucoplan in clinical settings.

7.R.4 Clinical positioning

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

The applicant's explanation:

The Japanese MG Clinical Guidelines recommend the use of oral corticosteroids, immunosuppressants such as calcineurin inhibitors (cyclosporin, tacrolimus) as first-line therapies for gMG. For patients who respond inadequately to the first-line therapy, physicians are advised to take the early fast-acting treatment (EFT) strategy, which aims at achieving both early improvement of symptoms and reduced use of oral corticosteroids. Plasmapheresis, IVIg, or molecular targeted therapies are used depending on the patient's condition.

Study MG0010 involving patients with gMG demonstrated the superiority of zilucoplan over placebo [see Section 7.R.2] and its safety results showed that zilucoplan has acceptable safety [see Section 7.R.3]. All the subjects enrolled in Study MG0010 had received prior treatment for gMG. Their prior therapies are the following: corticosteroids (86.8%; 151 of 174 subjects), immunosuppressants (72.4%; 126 of 174 subjects), IVIg (63.8%; 111 of 174 subjects), plasmapheresis (33.9%; 59 of 174 subjects), and acetylcholinesterase inhibitors (96.6%; 168 of 174 subjects). In Study MG0010, 96.0% (167 of 174) of subjects

were using the following concomitant gMG drugs: corticosteroids (63.2%; 110 of 174 subjects), immunosuppressants (51.1%; 89 of 174 subjects), acetylcholinesterase inhibitors (84.5%; 147 of 174 subjects), IVIg or plasmapheresis (0 subjects). The efficacy and safety of zilucoplan were confirmed regardless of the types of prior treatment and concomitant therapy.

In light of the clinical study results and pharmacology of zilucoplan, the applicant considers that zilucoplan can be positioned as a therapy used for the purpose of improving and/or maintaining gMG symptoms in patients with gMG who inadequately respond to corticosteroids or immunosuppressants.

PMDA's view:
Taking also into account the discussions in Sections 7.R.1 through 7.R.3 that contains reviews of the results from Study MG0010 and other data, zilucoplan can serve as a treatment option for patients with gMG who inadequately respond to corticosteroids or immunosuppressants, as explained by the applicant. In addition, whether to choose zilucoplan or other treatment options (excluding corticosteroids and immunosuppressants) can be decided by physicians with sufficient knowledge and experience in the treatment of gMG, including zilucoplan, depending on the symptoms and condition of the patient, while considering the differences in the safety profiles and in the dosage regimen between zilucoplan and other treatment options.

7.R.5 Indication

PMDA asked the applicant to explain the appropriateness of the proposed indication.

The applicant's explanation:
Study MG0010 was conducted in patients with anti-AChR-antibody positive gMG with specified severity according to the MG-ADL and QMG score, regardless of prior therapy, and the results demonstrated the efficacy and safety of zilucoplan. Therefore, the initially proposed indication was "generalized myasthenia gravis."

However, in the treatment algorithm for gMG, oral corticosteroids and immunosuppressants are recommended as first-line therapies. According to the protocol used at the time of enrollment, the criteria for MG-ADL and QMG scores did not allow enrollment of patients with mild gMG whose symptoms were likely to improve only with low-dose oral corticosteroids or acetylcholinesterase inhibitors. Study MG0010 enrolled no treatment-naïve patients, and the majority of subjects enrolled (73%) had prior therapy with corticosteroids or immunosuppressants but had no history of prior immunoglobulin therapy (intravenous or subcutaneous) or plasmapheresis on a regular basis. In Study MG0010, in the subgroup of patients who had prior therapy with corticosteroids or immunosuppressants but no history of prior immunoglobulin therapy (intravenous or subcutaneous) or plasmapheresis on a regular basis, the change from baseline in MG-ADL total score at Week 12 tended to be higher in the zilucoplan group than in the placebo group (−2.42 ± 0.50 in the placebo group and −4.66 ± 0.56 in the zilucoplan group; difference from placebo [95% CI], −2.24 [−3.54, −0.93]), and this trend was consistent with that of the overall population. The safety data also showed a trend consistent with

that of the overall population. Based on the above results, the indication for zilucoplan will be modified as "generalized myasthenia gravis (only in patients who inadequately respond to corticosteroids or nonsteroidal immunosuppressants)." In addition, in light of the clinical study results and the mechanism of action, zilucoplan has been shown to be effective in patients who are anti-AChR-antibody positive; therefore, the "Precautions Concerning Indication" section will include a cautionary statement to the effect that zilucoplan is indicated for patients who are anti-AChR-antibody positive.

PMDA's view:
Based on the patient population of Study MG0010, which demonstrated the efficacy and safety of zilucoplan, and on the treatment algorithm for gMG recommended in the guidelines available in Japan, the indication for zilucoplan should be "generalized myasthenia gravis (only in patients who inadequately respond to corticosteroids or nonsteroidal immunosuppressants)," and a cautionary statement to the effect that zilucoplan is indicated for patients who are anti-AChR-antibody positive should be included in the "Precautions Concerning Indication" section of the package insert.

The above conclusion by PMDA will be further discussed at the Expert Discussion.

7.R.6 Dosage and administration

PMDA asked the applicant to explain the appropriateness of the proposed dosage and administration.

The applicant's explanation:
The protocols of Studies MG0010 and MG0011 specified the use of a fixed dose by body weight band used in the 0.3 mg/kg group for ease of administration, as is the case of Study MG0009 [see Sections 7.3.1 and 7.3.2]. The results of the studies demonstrated the efficacy of zilucoplan in patients with gMG [see Section 7.R.2] and acceptable safety [see Section 7.R.3]. Therefore, the proposed dosage regimen was determined to be "the usual adult dosage is 0.3 mg/kg of zilucoplan administered as a subcutaneous injection once daily," as with that for Study MG0010; however, the use of the system of fixed dose by body weight band employed in Study MG0010, was considered appropriate (Table 44).

In addition, the applicant's considerations on the dosage for patients weighing <43 kg and those weighing >150 kg, which was to be determined by the principal investigator on an individual basis in Study MG0010 are presented. For the dosage for patients weighing <43 kg and those weighing ≥109 kg in Study MG0009 and patients weighing <43 kg and those weighing >150 kg in Studies MG0010 and MG0011, the protocol specified that the dose was to be determined by the principal investigator on an individual basis. Of the enrolled patients, 1 patient had a body weight <43 kg (Study MG0011) and a total of 5 patients had a body weight >150 kg (1 subject in Study MG0009, 3 subjects in Study MG0011, and 1 subject participated in both Studies MG0009 and MG0011). The patient weighing <43 kg received the same dose as that recommended for those weighing ≥43 kg and <56 kg (16.6 mg), and the patients weighing >150 kg received the same dose as that recommended for those weighing ≥77 kg and ≤150 kg (32.4 mg). In Study MG0010, 1 subject who had weighed ≤150 kg at

baseline and received 32.4 mg gained weight to be >150 kg at baseline for Study MG0011. The subject continued receiving the same dosage. The results showed that the plasma zilucoplan concentrations in subjects weighing <43 kg or >150 kg were within the range of distribution of subjects in the weight range ≥43 kg and <150 kg [see Section 6.R.2]. The efficacy of zilucoplan in subjects weighing <43 kg or >150 kg did not differ markedly from that seen in subjects in the other weight bands. The safety data showed that the subject weighing <43 kg developed 2 events of cystitis, and 1 event each of eczema, tinea infection, large intestine polyp, and herpes zoster. While large intestine polyp was classified as a serious adverse event, the event was considered unrelated to zilucoplan. Of the 5 subjects weighing >150 kg, 4 developed adverse events (each subject experienced at least one serious adverse event); however, the majority of events were mild to moderate in severity.

As described above, although only a small number of subjects weighing <43 kg or >150 kg were enrolled in Studies MG0009, MG0010, and MG0011, there were no clinically relevant differences in plasma zilucoplan concentrations, efficacy data, or safety data between subjects weighing <43 kg or >150 kg and subjects in the other body weight bands. Given this result and the outcomes of simulation based on the PPK model [see Section 6.R.2], the applicant considers it to administer the same dose to patients weighing <43 kg as that for patients weighing ≥43 kg and <56 kg, and the same dose to patients weighing >150 kg as that for patients weighing ≥77 kg and ≤150 kg.

Therefore, the proposed dosage regimen should be as follows.

Modified dosage and administration (draft)

The usual adult dosage of zilucoplan administered as a subcutaneous injection once daily is determined based on the table below.

Body weight	Dosage
<56 kg	16.6 mg
≥56 kg and <77 kg	23.0 mg
≥77 kg	32.4 mg

PMDA's view:

In light of the dosage regimen based on the body weight band as specified in the protocol of Study MG0010, which demonstrated the efficacy and safety of zilucoplan, as well as plasma zilucoplan concentrations, efficacy data, safety data, and other data from subjects weighing <43 kg or >150 kg enrolled in the clinical studies, the modified dosage and administration statement proposed by the applicant is acceptable.

7.R.7 Self-administration

In Study MG0010, the study drug was self-administered by the subject. PMDA asked the applicant to explain the efficacy and safety of zilucoplan in patients with gMG who self-administered zilucoplan.

The applicant's explanation:
In Study MG0010, after training at the study center, subjects were instructed to self-inject study drug doses under the supervision of healthcare professionals to ensure that the subject had adequately learned the self-injection technique. Thereafter, subjects were allowed to self-inject subsequent doses independently. In Study MG0010, all 174 subjects self-administered the study drug, and the efficacy and safety of zilucoplan were confirmed in such subjects [see Sections 7.R.2 and 7.R.3]. Study MG0011, in which subjects were able to participate after the completion of Study MG0010 and other studies, also required self-administration. Zilucoplan was self-administered by all 200 subjects in the study, and no significant safety or other problems were reported.

The above results indicate no evidence of efficacy or safety issues in the clinical studies in which patients with gMG self-injected doses of zilucoplan. A cautionary statement will be provided to the effect that zilucoplan can be self-administered under the supervision of the physician only after patients have undergone adequate training to ensure that they can self-inject zilucoplan appropriately.

PMDA's view:
Based on the applicant's explanation, there are no particular concerns about self-administration by patients with gMG who are judged to have acquired the correct self-injection technique after training in medical institutions.

7.R.8 Post-marketing investigations

The applicant plans to conduct a post-marketing surveillance covering all patients treated with zilucoplan to assess the safety (including long-term safety) and other aspects of zilucoplan in clinical settings.

PMDA's view:
Currently available data are those collected in only a small number of patients treated with zilucoplan for a limited treatment duration in the clinical studies; in addition, gMG is a rare disease in Japan. Given these and other factors, the long-term safety of zilucoplan, including the risk of meningococcal infections, in clinical settings in Japan, should be investigated through the post-marketing surveillance.

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

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

The inspection and assessment are currently underway. The results and conclusion by PMDA will be reported in Review Report (2).

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

The inspection is currently underway. The results and conclusion by PMDA will be reported in Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that zilucoplan has efficacy in the treatment of gMG, and that zilucoplan has acceptable safety in view of its benefits. Zilucoplan is clinically meaningful because it offers a new treatment option for patients with gMG.

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

Review Report (2)

August 9, 2023

Product Submitted for Approval

Brand Name	Zilbrysq Syringe for S.C. Injection 16.6 mg
	Zilbrysq Syringe for S.C. Injection 23.0 mg
	Zilbrysq Syringe for S.C. Injection 32.4 mg
Non-proprietary Name	Zilucoplan Sodium
Applicant	UCB Japan Co., Ltd.
Date of Application	December 8, 2022

List of Abbreviations

See Appendix.

1. Content of the Review

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

At the Expert Discussion, the expert advisors supported PMDA's conclusion on the efficacy of zilucoplan presented in Review Report (1).

1.1 Safety

The following comments were made by the expert advisors regarding safety. The expert advisors supported the PMDA's conclusion in Section "7.R.3 Safety" in Review Report (1).

- The following conclusion reached by the PMDA is appropriate: Patients being treated with zilucoplan should be closely monitored for the risks of infections including those caused by *Neisseria meningitidis* and other encapsulated bacteria, pancreatitis, increases in pancreatic enzymes, and serious hypersensitivity reactions.
- The safety of zilucoplan in Japanese patients with gMG is acceptable provided that (1) the safety measures against meningococcal infections are taken, as is the case of those implemented for approved C5 inhibitors, and (2) zilucoplan is only used under the supervision of a physician who is familiar with the diagnosis and treatment of gMG and is also fully capable of managing the risks associated with the use of zilucoplan at

a medical institution that can respond to such risks, in close coordination with a physician who is well versed with the diagnosis and treatment of meningococcal infections.

1.2 Clinical positioning and indication

The following comments were made by the expert advisors regarding clinical positioning and indication. The expert advisors supported the PMDA's conclusions in Sections "7.R.4 Clinical positioning" and "7.R.5 Indication."

- No treatment-naïve patients were enrolled in Study MG0010, which demonstrated the efficacy of zilucoplan. Further, the majority of subjects enrolled (73%) had prior therapy with corticosteroids or immunosuppressants but had no history of prior immunoglobulin therapy (intravenous or subcutaneous) or plasmapheresis on a regular basis. Based on the above and other findings as well as the treatment algorithm for gMG in Japan, zilucoplan can serve as a treatment option for patients with gMG who inadequately respond to corticosteroids or immunosuppressants. In addition, whether to choose zilucoplan or other treatment options (excluding corticosteroids and immunosuppressants) can be decided by physicians with sufficient knowledge and experience in the treatment of gMG, depending on the symptoms and condition of the patient, while considering the differences in the safety profiles and in the dosage regimen between zilucoplan and other treatment options.
- The following conclusions reached by the PMDA are appropriate: Given the treatment algorithm for gMG in Japan and various factors including the study population of Study MG0010, which demonstrated the efficacy of zilucoplan, the indication of zilucoplan should be "generalized myasthenia gravis (only in patients who inadequately respond to corticosteroids or nonsteroidal immunosuppressants)." In addition, a cautionary statement to the effect that zilucoplan is indicated for patients who are anti-AChR-antibody positive should be included in Section "5. Precautions Concerning Indication" of the package insert.

1.3 Dosage and administration

The following comment on the dosage regimen of zilucoplan was made by the expert advisors: Although there were very few patients weighing <43 kg enrolled in the clinical studies, based on the estimated blood concentrations as the results of simulation for patients weighing <43 kg receiving zilucoplan, and on the clinical study results in patients weighing <43 kg, there is no significant concern about the administration of the dose determined for the weight band ≥43 kg and <56 kg to patients weighing <43 kg.

The expert advisors supported the PMDA's conclusion in Section "7.R.6 Dosage and administration" in Review Report (1).

The change over time in the MG-ADL total score, the primary efficacy endpoint of Study MG0010, showed improvements at Week 1 and the treatment effect generally became stable between Week 8 and Week 12. Based on the results and other factors, PMDA concluded that a cautionary statement to the effect that if symptoms do not improve by Week 12, switching to another treatment should be considered. The expert advisors supported the PMDA's conclusion on this issue.

Based on the discussion in Section 7.R.6. in Review Report (1) and the above discussion at the Expert Discussion, PMDA instructed the applicant to include a cautionary statement in the "Precautions Concerning Dosage and Administration" section of the package insert to the effect that if the patient's symptoms do not improve by Week 12, switching to another treatment option should be considered. The applicant agreed with the instruction.

1.4 Risk management plan (draft)

At the Expert Discussion, the expert advisors supported the PMDA's conclusion in Section "7.R.8 Post-marketing investigations" in Review Report (1). PMDA has concluded that the risk management plan (draft) for zilucoplan should include the safety specifications presented in Table 68, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 69, and should conduct the general use results-survey presented in Table 70.

Table 68. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Meningococcal infections • Pancreatitis • Serious hypersensitivity	• Serious infections	• None
Efficacy specification		
• None		

Table 69. 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 • General use-results survey	• Disseminate data gathered during early post-marketing phase vigilance • Organize and disseminate information for healthcare professionals • Organize and disseminate information for patients

Table 70. Outline of use-results survey (draft)

Objective	To gather information on the safety and efficacy of zilucoplan in patients with gMG treated with zilucoplan in clinical settings
Survey method	All-case surveillance
Population	All patients with gMG treated with zilucoplan
Observation period	3 years
Planned sample size	150 patients
Main survey items	• Patient characteristics (e.g., age, body weight, medical history [history of thymoma, thymectomy, myasthenic crisis], comorbidities, status of vaccination with meningococcal vaccine, severity) • Prior therapy for gMG, concomitant drugs/therapies • Status of zilucoplan treatment • Adverse events • Pathogens responsible for infections including meningococcal infections (include serotype for *Neisseria meningitidis*) and other information • Efficacy assessment (MG-ADL total score, QMG total score)

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

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

The new drug application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that

there were no obstacles to conducting its review based on the application documents submitted. The inspection revealed the following errors in CTD 3.2.P.8.3, CTD 5.3.5.2.1, and CTD 5.3.5.2.2. Although they did not substantially affect the evaluation of the entire study, the errors were notified to the applicant as findings requiring corrective action:

Findings requiring corrective action

CTD 3.2.P.8.3

Applicant

- There were description errors in the application documents due to inadequate quality control of the documents.

CTD 5.3.5.2.1, 5.3.5.2.2

Sponsor

- The clinical study report was created using case report forms containing data that had not been confirmed by the principal investigator.

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

The new drug application data (CTD 5.3.5.1.2, CTD 5.3.5.2.1, and 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.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indication and dosage and administration shown below, with the following conditions. Since the product is a drug with a new active ingredient, the re-examination period is 8 years. The product is not classified as a biological product or a specified biological product. The drug product and its drug substance are both classified as powerful drugs.

Indication

Generalized myasthenia gravis (only in patients who inadequately respond to corticosteroids or nonsteroidal immunosuppressants)

Dosage and Administration

The usual adult dosage of zilucoplan administered as a subcutaneous injection once daily is determined based on the table below.

Body weight	Dosage
<56 kg	16.6 mg
≥56 kg and <77 kg	23.0 mg
≥77 kg	32.4 mg

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because data from Japanese clinical studies are very limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product to keep track of information on patient characteristics until data from a specified number of patients have been accrued. Furthermore, data on the safety and efficacy of the product should be collected as soon as possible, and measures to ensure proper use of the product should also be taken.
3. The applicant is also required to take necessary post-marketing measures, to ensure that the product will be administered only under the supervision of a physician who is familiar with the diagnosis and treatment of generalized myasthenia gravis and is also fully capable of managing the risks etc. associated with the product at a medical institution that can respond to such risks, in close coordination with a physician who is well versed with the diagnosis and treatment of meningococcal infections.

Appendix

List of Abbreviations

AChR	Acetylcholine Receptor
ADA	Antidrug antibody
A/G	Albumin/Globulins
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
BLQ	Below the limit of quantification
BMI	Body mass index
Boc	*tert*-Butoxycarbonyl
C3	Complement component C3
C4	Complement component C4
C5	Complement component C5
C6	Complement component C6
C7	Complement component C7
CCK	Cholecystokinin
CD	Circular dichroism spectroscopy
C_{max}	maximum observed Concentration
CPP	Critical process parameter
CQA	Critical Quality Attributes
CTD	Common Technical Document
Eculizumab	Eculizumab (genetical recombination)
EC_{90}	90% effective concentration
EFT	Early fast-acting treatment strategy
EG	Ethylene glycol
ELISA	Enzyme-linked Immunosorbent Assay
Fmoc	Fluorenylmethoxycarbonyl
FT-IR	Fourier transform infrared spectroscopy
GABA	Gamma amino butyric acid
GC	Gas chromatography
GC-MS	Gas chromatography-mass spectrometry
GGT	Gamma glutamyltransferase
gMG	generalized Myasthenia Gravis
HLT	High-Level Terms
HPLC	High performance liquid chromatography
HSA	Human serum albumin
IC_{50}	50% inhibitory concentration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICH M3(R2) Guidelines	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use M3(R2) Guidelines: Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (PFSB/ELD Notification No. 0219-4, dated February 19, 2010)
ICH Q1E Guidelines	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Q1E Guidelines: Evaluation for Stability Data (PFSB/ELD Notification No. 0603004, dated June 3, 2003)
Ig	Immunoglobulin
IVIg	Intravenous Immunoglobulin
K_D	Dissociation constant

LC-MS/MS	Liquid Chromatography-Tandem Mass Spectrometry
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MG	Myasthenia Gravis
MG-ADL	Myasthenia Gravis Activities of Daily Living
MGFA	Myasthenia Gravis Foundation of America
MG Clinical Guidelines	Japanese Clinical Guidelines 2022 for Myasthenia Gravis and Lambert-Eaton Myasthenic Syndrome. [in Japanese], edited by Japanese Society of Neurology Committee of Clinical Guidelines for Myasthenia Gravis/Lambert-Eaton Myasthenic Syndrome
mITT	modified Intention-to-Treat
MMRM	Mixed Model Repeated Measures
MS	Mass spectrometry
MuSK	Muscle-specific receptor tyrosine Kinase
NMR	Nuclear magnetic resonance spectroscopy
OC	Observed Cases
OX1	orexin-1
Pbf	2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl
PD	Pharmacodynamics
PEG	Polyethylene glycol
PFP	Pentafluorophenyl
pH	potential Hydrogen
Placebo / zilucoplan 0.1 mg/kg / zilucoplan 0.3 mg/kg	Subjects who were assigned to placebo in the main portion of Study MG0009, zilucoplan 0.1 mg/kg in the extension portion of Study MG0009, and received zilucoplan 0.3 mg/kg in Study MG0011
Placebo / zilucoplan 0.3 mg/kg	Subjects who were assigned to placebo in the main portion and zilucoplan 0.3 mg/kg in the extension portion of Study MG0009 and received zilucoplan 0.3 mg/kg in Study MG0011; or subjects who were assigned to placebo in Study MG0010 and received zilucoplan 0.3 mg/kg in Study MG0011
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	Population pharmacokinetics
PT	Preferred Term
QMG	Quantitative Myasthenia Gravis
Ravulizumab	Ravulizumab (genetical recombination)
sC5b-9	soluble C5b-9 complex
SDS-PAGE	Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SPR	Surface plasmon resonance
sRBC	Sheep Red Blood Cell
ULN	Upper limit of normal
UV	Ultraviolet spectroscopy
WoE	Weight of Evidence
Zilbrysq	Zilbrysq Syringe for S.C. Injection 16.6 mg, Zilbrysq Syringe for S.C. Injection 23.0 mg, Zilbrysq Syringe for S.C. Injection 32.4 mg
Zilucoplan	Zilucoplan Sodium
Zilucoplan 0.1 mg/kg / zilucoplan 0.1 mg/kg / zilucoplan 0.3 mg/kg	Subjects who were assigned to zilucoplan 0.1 mg/kg in both the main and extension portions of Study MG0009 and received zilucoplan 0.3 mg/kg in Study MG0011
Zilucoplan 0.3 mg/kg / zilucoplan 0.3 mg/kg	Subjects who were assigned to zilucoplan 0.3 mg/kg in both the main and extension portions of Study MG0009, or assigned to zilucoplan 0.3 mg/kg in Study MG0010, and received zilucoplan 0.3 mg/kg in Study MG0011