Report on the Deliberation Results

December 6, 2017

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

Brand Name	Soliris for Intravenous Infusion 300 mg
Non-proprietary Name	Eculizumab (Genetical Recombination) (JAN*)
Applicant	Alexion Pharma Godo Kaisha
Date of Application	March 22, 2017

Results of Deliberation

In its meeting held on December 4, 2017, the First Committee on New Drugs concluded that the partial change application for 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 re-examination period is 10 years.

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because data from Japanese clinical studies are limited, the applicant is required to conduct a use-results survey over a specified period, covering all patients treated with the product, to understand the characteristics of patients treated with the product and to obtain safety and efficacy data so as to take necessary measures for the product to be used properly.
3. The applicant is required to take necessary post-marketing measures so that the product is administered only under the supervision of physicians and at medical institutions with expertise in the diagnosis and treatment of generalized myasthenia gravis and capability for managing the risks, etc. of the product, and only in cooperation with physicians with expertise in the diagnosis and treatment of meningococcal infection.

**Japanese Accepted Name (modified INN)*

This English translation of this Japanese review report is intended to serve as reference material made available for the convenience of users. In the event of any inconsistency between the Japanese original and this English translation, the Japanese original shall take precedence. PMDA will not be responsible for any consequence resulting from the use of this reference English translation.

Review Report

November 24, 2017
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	Soliris for Intravenous Infusion 300 mg
Non-proprietary Name	Eculizumab (Genetical Recombination)
Applicant	Alexion Pharma Godo Kaisha
Date of Application	March 22, 2017
Dosage Form/Strength	Injection: Each 30-mL vial contains 300 mg of Eculizumab (Genetical Recombination)
Application Classification	Prescription drug, (4) Drugs with a new indication, (6) Drugs with a new dosage
Items Warranting Special Mention	Orphan drug (Drug Designation No. 358 of 2014 [*26 yaku*]; PSEHB/PED Notification No. 1208-1 dated December 8, 2014, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour, and Welfare)
Reviewing Office	Office of New Drug III

Results of Review

On the basis of data submitted, PMDA has concluded that the data submitted demonstrate the efficacy of the product in the treatment of generalized myasthenia gravis (only for symptoms uncontrollable with high-dose intravenous immunoglobulin therapy or plasmapheresis) and 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.

This English translation of this Japanese review report is intended to serve as reference material made available for the convenience of users. In the event of any inconsistency between the Japanese original and this English translation, the Japanese original shall take precedence. PMDA will not be responsible for any consequence resulting from the use of this reference English translation.

Indications

Reduction of hemolysis in patients with paroxysmal nocturnal hemoglobinuria

Inhibition of thrombotic microangiopathy in patients with atypical hemolytic uremic syndrome

Treatment of patients with generalized myasthenia gravis (only for symptoms uncontrollable with high-dose intravenous immunoglobulin therapy or plasmapheresis)

(Underline denotes additions.)

Dosage and Administration

Reduction of hemolysis in patients with paroxysmal nocturnal hemoglobinuria

The usual adult dosage is 600 mg as Eculizumab (Genetical Recombination) given as an intravenous infusion weekly for a total of 4 doses, followed 1 week later (4 weeks after the first dose) by 900 mg given every 2 weeks thereafter.

Inhibition of thrombotic microangiopathy in patients with atypical hemolytic uremic syndrome

Eculizumab (Genetical Recombination) is usually administered as an intravenous infusion according the schedules below.

Age or body weight	Induction phase	Maintenance phase
≥18 years old	900 mg weekly × 4 doses	1200 mg every 2 weeks, from 4 weeks after the first dose
<18 years old		
≥40 kg	900 mg weekly × 4 doses	1200 mg every 2 weeks, from 4 weeks after the first dose
≥30 kg and <40 kg	600 mg weekly × 2 doses	900 mg every 2 weeks, from 2 weeks after the first dose
≥20 kg and <30 kg	600 mg weekly × 2 doses	600 mg every 2 weeks, from 2 weeks after the first dose
≥10 kg and <20 kg	600 mg weekly × 1 dose	300 mg every 2 weeks, from 1 week after the first dose
≥5 kg and <10 kg	300 mg weekly × 1 dose	300 mg every 3 weeks, from 1 week after the first dose

Treatment of patients with generalized myasthenia gravis (only for symptoms uncontrollable with high-dose intravenous immunoglobulin therapy or plasmapheresis)

The usual adult dosage is 900 mg of Eculizumab (Genetical Recombination) given as an intravenous infusion weekly for a total of 4 doses, followed 1 week later (4 weeks after the first dose) by 1200 mg given every 2 weeks thereafter.

(Underline denotes additions.)

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because data from Japanese clinical studies are limited, the applicant is required to conduct a use-results survey over a specified period, covering all patients treated with the product, to understand the characteristics of patients treated with the product and to obtain safety and efficacy data so as to take necessary measures for the product to be used properly.
3. The applicant is required to take necessary post-marketing measures so that the product is administered only under the supervision of physicians and at medical institutions with expertise in the diagnosis and treatment of generalized myasthenia gravis and capability for managing the risks, etc. of the product, and only in cooperation with physicians with expertise in the diagnosis and treatment of meningococcal infection.

Attachment

Review Report (1)

October 20, 2017

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.

Product Submitted for Approval	
Brand Name	Soliris for Intravenous Infusion 300 mg
Non-proprietary Name	Eculizumab (Genetical Recombination)
Applicant	Alexion Pharma Godo Kaisha
Date of Application	March 22, 2017
Dosage Form/Strength	Injection: Each 30- mL vial contains 300 mg of Eculizumab (Genetical Recombination).
Proposed Indications	Reduction of hemolysis in patients with paroxysmal nocturnal hemoglobinuria Inhibition of thrombotic microangiopathy in patients with atypical hemolytic uremic syndrome <u>Treatment of patients with generalized myasthenia gravis (only for intractable patients who have inadequate response to existing therapies or are inadequately controlled with prior therapies)</u> (Underline denotes additions.)
Proposed Dosage and Administration	**Reduction of hemolysis in patients with paroxysmal nocturnal hemoglobinuria** The usual adult dosage is 600 mg of Eculizumab (Genetical Recombination) given as an intravenous infusion weekly for a total of 4 doses, followed 1 week later (4 weeks after the first dose) by 900 mg given every 2 weeks thereafter. **Inhibition of thrombotic microangiopathy in patients with atypical hemolytic uremic syndrome** Eculizumab (Genetical Recombination) is usually administered as an intravenous infusion according to the schedules below.

Age or body weight	Induction phase	Maintenance phase
≥18 years old	900 mg weekly × 4 doses	1200 mg every 2 weeks, from 4 weeks after the first dose
<18 years old		
≥40 kg	900 mg weekly × 4 doses	1200 mg every 2 weeks, from 4 weeks after the first dose
≥30 kg and <40 kg	600 mg weekly × 2 doses	900 mg every 2 weeks, from 2 weeks after the first dose
≥20 kg and <30 kg	600 mg weekly × 2 doses	600 mg every 2 weeks, from 2 weeks after the first dose
≥10 kg and <20 kg	600 mg weekly × 1 dose	300 mg every 2 weeks, from 1 week after the first dose
≥5 kg and <10 kg	300 mg weekly × 1 dose	300 mg every 3 weeks, from 1 week after the first dose

Treatment of patients with generalized myasthenia gravis (only for intractable patients who have inadequate response to existing therapies or are inadequately controlled with prior therapies)

The usual adult dosage is 900 mg of Eculizumab (Genetical Recombination) given as an intravenous infusion weekly for a total of 4 doses, followed 1 week later (4 weeks after the first dose) by 1200 mg given every 2 weeks thereafter.

(Underline denotes additions.)

Table of Contents

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

Eculizumab (Genetical Recombination) is a humanized monoclonal antibody that binds with high affinity for human complement C5. Eculizumab was approved in Japan for "reduction of hemolysis in patients with paroxysmal nocturnal hemoglobinuria (PNH)" in April 2010 and "inhibition of thrombotic microangiopathy in patients with atypical hemolytic uremic syndrome (aHUS)" in September 2013.

Outside Japan, as of September 2017, eculizumab has been approved in 49 countries and regions including the US and Europe, and for the treatment of generalized myasthenia gravis (gMG) in Europe (28 countries).

In Japan, a clinical study in patients with gMG started in [redacted] 20[redacted]. Based on the study results, which demonstrated the efficacy and safety of eculizumab, the applicant filed this partial change application. Eculizumab was designated as an orphan drug on December 8, 2014, with an intended indication of refractory gMG (Drug Designation No. 358 of 2014 [*26 yaku*]).

Approved treatment options for myasthenia gravis (MG) in Japan include corticosteroids (prednisolone, dexamethasone, etc.), calcineurin inhibitors (cyclosporine and tacrolimus hydrate), polyethylene glycol treated human normal immunoglobulin, and cholinesterase inhibitors (pyridostigmine bromide, ambenonium chloride, etc.).

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

The present application is intended for a new indication and a new dosage, and no data relating to the quality of eculizumab were submitted.

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

The present application is intended for a new indication and a new dosage. The non-clinical pharmacology data submitted include published literature on primary pharmacodynamics and the results from a pharmacodynamic drug interaction study. Because eculizumab does not bind to rat C5 (CTD 4.2.1.1.6 for the initial application), a mouse anti-rat C5 monoclonal antibody was used in rat models.

3.1 Primary pharmacodynamics (CTD 4.3.6: *J Immunol.* 2007;179:8562-7)

MG was induced in rats by intraperitoneally injecting a rat anti-mouse muscle acetylcholine receptor (AChR) monoclonal antibody (0.24 μg/g). In 24 hour's time, the rats received a mouse anti-rat C5 monoclonal antibody (5 mg) intraperitoneally. Muscle strength[1)] measured 1 and 2 days later showed improvement.

MG was induced in rats by intraperitoneally injecting a rat anti-mouse muscle AChR monoclonal antibody (0.24 μg/g). In 24 hour's time, the rats received a mouse anti-rat C5 monoclonal antibody (5 mg) intraperitoneally. Hemolytic reaction was measured by reacting sheep erythrocytes with serum 2 and 3 days

1) Muscle strength was rated based on the following 5-point scale: 0, able to grip and lift the cage lid; 1, able to grip but unable to lift the cage lid; 2, unable to grip the cage lid; 3, unable to grip the cage lid and has forelimb paralysis; 4, moribund.

after the treatment. The rats treated with the anti-C5 monoclonal antibody showed reduced hemolytic reaction in serum.

Microscopic observation of the immunofluorescence-stained neuromuscular junction (NMJ) showed reduced C9 deposition in the rats treated with the anti-C5 monoclonal antibody.

These results suggested that the injection of the mouse anti-rat C5 monoclonal antibody inhibited serum C5 activity. The observation of the NMJ from the rats treated with the mouse anti-rat C5 monoclonal antibody using electron microscopy showed no evidence of MG (e.g., simplified junctional folds on the postsynaptic membrane, widened synaptic clefts) observed in rats untreated with the antibody.

3.2 Pharmacodynamic drug interactions (Reference CTD 4.2.4.1.4)

Chicken red blood cells were incubated with healthy human serum to assess the impact of cyclosporine (1100 ng/mL), tacrolimus (40 ng/mL), and intravenous immunoglobulin (IVIG) (21 or 25 mg/mL) on the C5 inhibitory effect of eculizumab (0, 2, 4, and 8 μg/mL) by measuring hemolytic activity in the serum. None of these drugs affected the inhibitory effect of eculizumab. Daudi cells (a human Burkitt's lymphoma-derived cell line) were mixed with natural killer cells isolated from healthy humans to evaluate the impacts of eculizumab (0.2-100 μg/mL) on the antibody-dependent cellular cytotoxicity (ADCC) of rituximab (genetical recombination) (10 μg/mL); no impacts were noticed. In addition, the impact of eculizumab on the complement-dependent cytotoxicity was assessed in Daudi cells opsonized by rituximab (genetical recombination) (10 μg/mL); treatment with eculizumab [redacted] μg/mL completely inhibited the complement-dependent cytotoxicity.

3.R Outline of the review conducted by PMDA

3.R.1 Mechanism of action of eculizumab

PMDA asked the applicant to explain the mechanism of action of eculizumab, including the differences from existing MG drugs, in light of the pathogenic mechanism of MG.

The applicant's explanation about the pathogenic mechanism of MG:

- MG is an autoimmune disease mediated by autoantibodies that bind to components of the NMJ, such as AChR, muscle-specific receptor tyrosine kinase (MuSK), and low-density lipoprotein receptor-related protein 4 (Lrp4). The most common autoantigen is AChR, with about 90% of patients with MG carrying anti-AChR antibodies (CTD 5.4.62: *Biochim Biophys Acta*. 2015;1852:651-7).
- Autoantibodies to AChR are predominantly Immunoglobulin G (IgG) 1 and IgG3 subclasses. These anti-AChR antibodies recognize AChR at the NMJ, induce uncontrolled terminal complement activation on the surfaces of nerves and muscle cells, and deplete AChR, thereby compromising neuromuscular transmission (CTD 5.4.157: *Autoimmun Rev.* 2013;12:904-11). MG induced by immunization with AChR was more severe in C5-deficient mice than in normal mice (*J Immunol.* 1988;140:2589-92), and C3- or C4-deficient mice were resistant to the induction of MG by the subcutaneous injection of AChR (*J Immunol.* 2003;171:3847-54). These suggest that the classical

complement pathway is considered to play a role in the development of anti-AChR antibody-associated MG.

- Complement activation is considered not involved in the development of anti-MuSK antibody-positive MG (*J Anat.* 2014; 224: 29-35), because (a) antibodies against muscle-specific tyrosine kinase (MuSK) belong to the IgG4 subclass which do not activate complements (*Ann Neurol.* 2004;55:580-4); (b) no complement deposition was detected in the NMJ in patients with anti-MuSK antibody-positive MG (*Neurology.* 2004;62:1945-50); and, (c) in an animal model of anti-MuSK antibody-positive MG, the disease symptoms developed in the absence of complements (*Am J Pathol.* 2012;180:798-810). In the development of antibodies against Lrp4, complements may play a role (*Rinsho Shinkeigaku.* 2012;52:1303-5); however, patients with anti-Lrp4 antibody-positive MG represent only 3% of all patients with MG (*Ann Neurol.* 2011;69:418-22), and the clinical significance and importance of the antibodies as the etiology of the disease have not been completely clarified (*F1000Res.* 2016;5:1513).

The applicant's explanation about the mechanism of action of existing MG drugs, including corticosteroids, calcineurin inhibitors (tacrolimus hydrate and cyclosporine), and human IgG, as well as cholinesterase inhibitors (e.g., pyridostigmine bromide, ambenonium chloride) that are secondarily administered:

- Corticosteroids bind to DNA (e.g., glucocorticoid response element) in T cells, thereby inducing apoptosis in T cells and inhibiting the production of inflammatory cytokines to exert their immunosuppressive effects (CTD 5.4.86: *Curr Neuropharmacol.* 2011;9:468-77; *Cell Mol Life Sci.* 2006;60-72; *Science.* 1995:270;283-6).
- Calcineurin inhibitors act on calcineurin, which is essential for dephosphorylation of the nuclear factor of activated T cells, and inhibit the activation of T cells to exert their immunosuppressive effects (*Immunol Today.* 1992;13:136-42).
- Although the mechanism of action of human IgG has not been fully clarified, one of published theories indicates that IgG accelerates the expression of inhibitory Fc receptors by binding to the receptors on antigen-presenting cells and reduces the half-lives of autoreactive antibodies (*Pediatrics.* 2002;110:467-8).
- Cholinesterase inhibitors activate AChR by increasing acetylcholine at the NMJ, thereby accelerating the activation and contraction of muscles (CTD 5.4.143: *Eur J Neurol.* 2010;17:893-902). Cholinesterase inhibitors are effective only in patients with early-stage or mild MG in whom a sufficient amount of AChR still remains (CTD 5.4.53: *Autoimmun Rev.* 2007;6:373-8).

Based on the above explanation, and in view of the published article on primary pharmacodynamics [see Section 3.1 Primary pharmacodynamics], eculizumab, unlike existing MG drugs, is considered to block the inflammatory response by inhibiting C5 activation at the NMJ in patients with anti-AChR antibody-positive MG, and improve the symptoms of the disease.

Complement C5 has genetic polymorphisms. About 3% of Japanese patients have gene polymorphisms (c.2654G>A, c.2653C>T) associated with a markedly decreased binding affinity of eculizumab for C5 (*N Engl*

J Med. 2014; 370: 632-9). The possibility remains that the effect of eculizumab may be attenuated in patients with such polymorphisms due to its pharmacological action. Nevertheless, the above-mentioned result was yielded from a study with a limited sample size, with no published articles supporting the outcome, and the prevalence of these polymorphisms is low. Therefore, the impact of C5 polymorphisms on the efficacy of eculizumab has not been clarified. There are no commercially available diagnostic agents to measure C5 gene polymorphisms or no testing companies that undertake the measurement of these polymorphisms at present. Therefore, the use of eculizumab may be started without separating or excluding patients with the C5 gene polymorphisms associated with the decreased binding affinity of eculizumab for C5, with a cautionary note given in the package insert to advise to consider discontinuation of eculizumab for patients not responding to the therapy over a specified time period. When a C5 gene polymorphisms test becomes available in Japan in the future, the applicant wishes to discuss with PMDA again about the target patient population of eculizumab.

PMDA asked the applicant to explain the pharmacodynamic drug interactions between eculizumab and other existing MG drugs, in consideration of the clinical positioning of eculizumab [see Section 7.R.5].

The applicant's explanation:
Eculizumab is intended to be used concomitantly with existing MG drugs in the treatment of patients with gMG [see Section 7.R.5], while eculizumab is expected to be effective alone, given its mechanism of action and the fact that treatment with eculizumab improved muscle strength in MG-induced rats [see Section 3.1]. Since the mechanism of action of eculizumab differs from that of existing MG drugs, eculizumab is pharmacologically unlikely to cause pharmacodynamic drug interactions with existing MG drugs to be used concomitantly. An assessment of the pharmacodynamic interactions between eculizumab and cyclosporine, tacrolimus hydrate, and human IgG showed no clear impacts (Reference CTD 4.2.1.4.1), indicating that eculizumab is unlikely to have clinically important pharmacodynamic interactions with existing MG drugs.

PMDA's view:
The applicant’s discussion on the action mechanism of eculizumab in patients with MG based on the results of non-clinical pharmacology studies is adequate. In light of its mechanism of action, the use of eculizumab should be limited to patients with MG who are anti-AChR antibody-positive as in the Europe, and this should be specifically stated in the package insert. In regard to C5 gene polymorphisms that have been reported to decrease binding affinity of eculizumab for C5, the impact of C5 gene polymorphisms on the efficacy of eculizumab has been studied across the world and remains inconclusive. For this reason, and considering the seriousness of the target disease of eculizumab, it is inevitable to initiate eculizumab therapy without performing prior genetic testing using a sequencer, etc., while giving a cautionary note in the package insert that the discontinuation of eculizumab be considered for patients inadequately responding to the therapy over a specified period. Nevertheless, the possibility still remains that the C5 gene polymorphisms may affect the efficacy of eculizumab, and the impacts of these C5 gene polymorphisms on the binding activity of eculizumab should be promptly assessed in cooperation with related academic societies. If eculizumab is revealed to have little binding activity to C5 in patients carrying the gene polymorphisms, the appropriateness of eculizumab

therapy for these patients and the necessity of testing for C5 gene polymorphisms prior to the eculizumab therapy should be immediately discussed.

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

The present application is intended for a new indication and a new dosage. No data relating non-clinical pharmacokinetic were submitted.

5. Toxicity and Outline of the Review Conducted by PMDA

The present application is intended for a new indication and a new dosage. No data relating to the toxicity of eculizumab were submitted.

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

6.1 Summary of biopharmaceutic studies and associated analytical procedures

No data from biopharmaceutic studies were submitted.

Serum concentrations of eculizumab and free C5 were measured using Enzyme-linked Immunosorbent Assay (ELISA) (lower limits of quantification, 9.38 to 9.4 μg/mL and 0.0274 μg/mL, respectively). The serum concentrations of anti-eculizumab antibodies were measured using an electro-chemiluminescent immunoassay (lower limit of quantification, 2 to 6.26 μg/mL).

6.2 Clinical pharmacology

The applicant submitted evaluation data, in the form of results from a foreign phase II study in non-Japanese patients (CTD 5.3.5.1.3, Study C08-001), a global phase III study in Japanese and non-Japanese patients (CTD 5.3.5.1.1, Study ECU-MG-301), and its long-term extension study (CTD 5.3.5.2.1, Study ECU-MG-302). The main results from pharmacokinetic studies are summarized in the following subsection.

6.2.1 Studies in patients

Eculizumab was intravenously administered to non-Japanese patients with gMG (13 patients evaluable for pharmacokinetics) at 600 mg weekly for 4 doses (Weeks 0, 1, 2, and 3), followed by 900 mg every 2 weeks for 7 doses (Weeks 4 to 16). The trough serum eculizumab concentrations were 166 ± 80.1 at Week 4 and 155 ± 109 μg/mL at Week 16. No patients had serum anti-eculizumab antibodies (CTD 5.3.5.1.3, Study C08-001).

Eculizumab was intravenously administered to Japanese and non-Japanese patients with gMG (62 patients evaluable for pharmacokinetics) at 900 mg weekly for 4 doses (Weeks 0, 1, 2, and 3), followed by 1200 mg every 2 weeks for 12 doses (Weeks 4 to 26). The trough serum concentrations of eculizumab and free C5 are presented in Table 1. Trough serum eculizumab concentrations tended to be higher in Japanese patients than in non-Japanese patients, and trough serum free C5 concentrations tended to be lower in Japanese patients. The differences in the trough serum concentrations of eculizumab and free C5 between Japanese and non-Japanese

patients may be attributed to the lower body weight in Japanese patients than in the entire study population. However, the distributions of the trough serum concentrations of eculizumab and free C5 in Japanese patients overlapped with those in non-Japanese patients, suggesting no substantial ethnic differences in the pharmacokinetics of eculizumab. Serum anti-eculizumab antibodies were detected in 3 patients in the placebo group and 1 patient in the eculizumab group. One of the 3 patients in the placebo group had neutralizing antibodies. The trough serum eculizumab concentration in this study (Study ECU-MG-301) was ≥2 times higher than that in the phase II study (CTD 5.3.5.1.3, Study C08-001). Although this difference may be attributed to the different analytical procedures used in the studies, it has not been clearly explained (CTD 5.3.5.1.1, Study ECU-MG-301).

Table 1. Trough serum concentrations of eculizumab and free C5 in Japanese and non-Japanese patients with gMG receiving multiple intravenous doses of eculizumab

Time point	Eculizumab		Free C5	
	Japanese	Non-Japanese	Japanese	Non-Japanese
Week 0	-	-	121.0 ± 18.7 (3)	121.8 ± 25.1 (57)
Week 4	475 ± 82 (3)	368 ± 136 (56)	0.025 ± 0.010 (3)	0.95 ± 6.69 (54)
Week 26	445 ± 122 (3)	336 ± 173 (54)	0.019 ± 0.0099 (3)	1.17 ± 6.71 (52)

Mean ± SD (μg/mL) (n)

6.R Outline of the review conducted by PMDA

6.R.1 Pharmacokinetic interactions

Eculizumab may be used concomitantly with other MG drugs in view of its clinical positioning [see Section 7.R.5 Clinical positioning], and is a humanized monoclonal antibody known to deplete other antibodies (CTD 5.4.160, *Adv Neurol.* 2001;88:159-88). PMDA asked the applicant to explain the pharmacokinetic interactions between eculizumab and concomitant IVIG.

The applicant's explanation:

When used concomitantly with long-term IVIG, the clearance of eculizumab, as with other antibodies, was shown to increase by ≥50% (*J Peripher Nerv Syst.* 2011;16:84-91). If the clearance of eculizumab increases by 50%, the trough serum eculizumab concentration (median [95% confidence interval]) during the maintenance phase is estimated to decrease by 33% (from 284 [110, 662] μg/mL to 189 [73, 442] μg/mL), and the trough serum C5 concentration to increase by 489% (from 0.0095 [0.0002, 0.61] μg/mL to 0.056 [0.0014, 3.5] μg/mL). In the global phase III study (CTD 5.3.5.1.1, Study ECU-MG-301), the concomitant use of IVIG was permitted only when clinical deterioration was evident; thus, the impact of IVIG on the efficacy of eculizumab was not systematically evaluated. Therefore, the decrease in serum eculizumab concentration in concomitant use with IVIG should be highlighted in the package insert.

PMDA's view:

The applicant's explanation is acceptable. Information on the efficacy of eculizumab used concomitantly with IVIG should be collected further after market launch.

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 from the clinical studies presented in Table 2. The main results of these studies are summarized in the following subsections.

Table 2. Summary of clinical studies on the efficacy and safety of eculizumab

Data type	Region	Study identifier CTD	Phase	Subjects	N	Dosage regimen	Main endpoints
Evaluation data	Foreign	C08-001 5.3.5.1.3	II	Refractory gMG	14	Intravenous placebo or eculizumab 600 mg weekly for 4 doses (Weeks 0, 1, 2, and 3), followed by placebo or eculizumab 900 mg at Week 4 and every 2 weeks thereafter for 7 doses (Weeks 4 to 16)	Efficacy Safety Pharmacokinetics
	Global	ECU-MG-301 5.3.5.1.1	III	Refractory gMG	126[a)]	Intravenous placebo or eculizumab 900 mg weekly for of 4 doses (Weeks 0, 1, 2, and 3), followed by placebo or eculizumab 1200 mg at Week 4 and every 2 weeks thereafter for 12 doses (Weeks 4 to 26)	Efficacy Safety Pharmacokinetics
	Global	ECU-MG-302 5.3.5.2.1	Long-term extension	Refractory gMG	117	Intravenous placebo or eculizumab 900 mg weekly for 4 doses (Weeks 0, 1, 2, and 3), followed by eculizumab 1200 mg at Week 4 and every 2 weeks thereafter for up to 4 years	Efficacy Safety Pharmacokinetics

a) Number of randomized patients

7.1 Global phase III study (CTD 5.3.5.1.1, Study ECU-MG-301, April 2014 to February 2016)

A placebo-controlled, randomized, double-blind, parallel group, comparative study was conducted in 17 countries[2)] to evaluate the efficacy, safety, and pharmacokinetics of eculizumab in patients with refractory gMG[3)] who were anti-AChR antibody-positive (target sample size, 46 patients/group and 92 patients in total) [for pharmacokinetics, see Section 6.2 Clinical pharmacology].

The patients received intravenous doses of placebo or eculizumab 900 mg weekly for 4 times (Weeks 0, 1, 2, and 3), followed by 1200 mg at Week 4 and every 2 weeks thereafter for 12 times. The evaluation duration was 26 weeks. After the completion of the study period, the patients were allowed to proceed to a long-term extension study (CTD 5.3.5.2.1, Study ECU-MG-302) to continue eculizumab therapy at their own wish.

Of 126 randomized patients (63 in the placebo group, 63 in the eculizumab group), 125 (63, 62) were included in both the safety analysis set and the Full Analysis Set (FAS), except 1 patient in the eculizumab group who did not receive the study drug. Efficacy analyses were performed on the FAS. A total of 8 patients (2, 6) discontinued the study. The major reasons for discontinuation were adverse events in 4 patients (0, 4) and consent withdrawal in 3 patients (2, 1).

2) The US, Canada, Argentina, Brazil, Belgium, Denmark, Spain, Finland, the UK, Italy, Netherlands, Sweden, the Czech Republic, Hungary, Turkey, South Korea, and Japan

3) Patients with MG of Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II to IV with an MG-ADL total score of ≥6 at screening, and:
(i) failed to respond to over ≥1 year-long therapy with ≥2 immunosuppressants or
(ii) failed to respond to ≥1 immunosuppressant(s) and require plasmapheresis or IVIG on a regular basis for the management of muscle weakness, at least once every 3 months in the past 12 months

Table 3 shows changes from baseline in Myasthenia Gravis Activities of the Daily Living Profile (MG-ADL) total score[4)] at Week 26, the primary endpoint prespecified by the protocol, and the clinical event (rescue therapy) in the FAS. A rank analysis based on the change in MG-ADL total score and the clinical event achieved a statistically significant difference between the eculizumab group and the placebo group ($P = 0.0089$, Worst-Rank analysis of covariance [ANCOVA], defined in the protocol and the statistical analysis plan [SAP] version 1.0[5)]).

Table 3. Changes from baseline in MG-ADL total score at Week 26 (FAS, LOCF)

	MG-ADL total score[a)]			Clinical event[b)]	Worst-Rank analysis[c)]	
	Baseline	Week 26	Change	Rescue therapy	Rank[d)]	Difference between the groups[e)]
Placebo	9.9 ± 2.64 (51) 9.0 (5, 18)	7.0 ± 3.36 (51) 6.0 (2, 16)	-2.8 ± 3.07 (51) -2.0 (-8, 7)	62.2 ± 55.40 (12) 43.5 (7, 178)	70.8 ± 4.38 (63)	-16.6 [-28.90, -4.23] $P = 0.0089$
Eculizumab	10.3 ± 3.06 (56) 10.0 (5, 18)	5.6 ± 4.11 (56) 5.5 (0, 15)	-4.7 ± 4.20 (56) -4.5 (-15, 4)	95.7 ± 71.50 (6) 99.5 (1, 174)	54.2 ± 4.42 (62)	

a) Top, mean ± SD (n); bottom, median (minimum, maximum); in patients requiring no rescue therapy
b) Time (days) to the event; top, mean ± SD (n), bottom, median (minimum, maximum)
c) Worst-Rank analysis defined as the primary analysis in the protocol and the SAP version 1.0[5)]
d) Adjusted mean ± SD of the rank[5)] (based on ANCOVA) (n)
e) Top, difference between the treatment groups; middle, 95% confidence interval for the difference between the groups; bottom, *P* value for comparison of the treatment groups

The results of the efficacy analysis performed according to the SAP amended before unblinding, in response to the comments from the Food and Drug Administration (FDA) concerning the analytical procedures in the study [see Section 7.R.1 Analytical procedures in the global phase III study], are presented in Table 4. A trend toward greater improvement in MG symptoms in the eculizumab group relative to the placebo group was noticed, although there was no statistically significant difference between the groups ($P = 0.0698$, Worst-Rank ANCOVA defined in the SAP version 3[6)]).

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

5) Worst-Rank analysis defined in the protocol and the SAP version 1.0: Patients were ranked from the worst in the following patient populations in that order, to perform an analysis based on an ANCOVA model including the rank as a response variable, the treatment group and MGFA class (Class IIa, IIIa/IVa/IIb or IIIb/ IVb) as factors, and the MG-ADL total score at baseline as a covariate: (a) patients who received rescue therapy (ranked in ascending order of the number of days to rescue therapy), and (b) patients who required no rescue therapy (ranked in ascending order of the change from baseline in MG-ADL total score at Week 26 [LOCF]).

6) Worst-Rank analysis specified in the SAP version 3.0: Patients were ranked from the worst in the following patient populations in that order, to perform an analysis based on an ANCOVA model including the rank as a response variable, the treatment group and MGFA class (Class IIa, IIIa/IVa/IIb or IIIb/IVb) as factors, and the MG-ADL total score at baseline as a covariate: (a) patients who died by Week 26 (ranked in ascending order of the number of days to death), (b) patients who experienced MG crisis (ranked in ascending order of the number of days to MG crisis), (c) patients who received rescue therapy or discontinued the study (ranked in ascending order of the number of days to rescue therapy or study discontinuation (whichever came first, if both events occurred), and (d) patients who completed the 26-week study treatment without requiring rescue therapy (ranked in ascending order of the improvement from baseline in MG-ADL total score at Week 26 [LOCF]).

Table 4. Changes from baseline in MG-ADL total score at Week 26 (FAS)

	MG-ADL total score[a)]			Clinical event[b)]		Worst-Rank analysis[c)]	
	Baseline	Week 26	Change	MG crisis	Rescue therapy or study discontinuation	Rank[d)]	Difference between the groups[e)]
Placebo	9.9 ± 2.64 (51) 9.0 (5, 18)	7.0 ± 3.36 (51) 6.0 (2, 16)	-2.8 ± 3.07 (51) -2.0 (-8, 7)	-	62.2 ± 55.40 (12) 43.5 (7, 178)	68.3 ± 4.49 (63)	-11.7 [-24.33, 0.96] *P* = 0.0698
Eculizumab	10.1 ± 3.00 (52) 10.0 (5, 18)	5.4 ± 4.05 (52) 5.0 (0, 15)	-4.7 ± 4.32 (52) -4.5 (-15, 4)	127.0 (1)	87.9 ± 60.76 (9) 85.0 (1, 174)	56.6 ± 4.53 (62)	

a) Top, mean ± SD (n); bottom, median (minimum, maximum); in patients completing the 26-week treatment with the study drug, without requiring rescue therapy
b) Time (days) to the event; top, mean ± SD (n); bottom, median (minimum, maximum)
c) Worst-Rank analysis, defined as the primary analysis in the SAP version 3.0[6)]
d) Adjusted mean ± SD of the rank[6)] (based on ANCOVA) (n)
e) Top, difference between the treatment groups; middle, 95% confidence interval for the difference between the groups; bottom, *P* value for the comparison of the treatment groups

Adverse events (including laboratory abnormalities) occurred in 88.9% (56 of 63) of patients in the placebo group and 85.5% (53 of 62) of patients in the eculizumab group. No deaths occurred during the study period. However, 1 patient in the eculizumab group who was withdrawn from the study due to MG crisis on Day 128 died 89 days after the last dose of eculizumab; for the MG crisis, a causal relationship to the study drug could not be ruled out. The serious adverse events other than death reported in the study are summarized in Table 5.

Table 5. Serious adverse events other than death reported in Study ECU-MG-301

Placebo	Myasthenia gravis in 5 patients,[a)] myasthenia gravis/general physical health deterioration[*]/apnoea, gastroenteritis/lymphocyte count decreased/urinary tract infection bacterial, myasthenia gravis/upper respiratory tract infection,[*] myasthenia gravis[*]/intentional overdose,[*] pulmonary embolism,[*] tonsillitis,[*] hyperglycaemia, gastritis,[*] varicella,[*] deep vein thrombosis, cholecystitis acute, and upper respiratory tract infection in 1 patient each (18 patients in total)
Eculizumab	Myasthenia gravis in 4 patients,[a)] myasthenia gravis/pyrexia[*]/lymphopenia, bacteraemia[*]/endocarditis,[*] intestinal perforation[*]/diverticulitis,[*] prostate cancer/metastases to bone, and pyrexia[*] in 1 patient each (8 patients in total)

[*] Events for which a causal relationship to the study drug could not be ruled out
a) A causal relationship to the study drug could not be ruled out in 1 patient.

The incidences of adverse events (including laboratory abnormalities) for which a causal relationship to the study drug could not be ruled out were 52.4% (33 of 63 patients) in the placebo group and 66.1% (41 of 62 patients) in the eculizumab group. The major events were nausea (9 patients in the placebo group, 8 patients in the eculizumab group), upper respiratory tract infection (6, 8), diarrhoea (4, 7), headache (7, 5), dizziness (3, 4), myalgia (2, 4), and vomiting (4, 1).

No clinically important changes in vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) were reported. Electrocardiogram revealed a left axis deviation that was consistent with a diagnosis of left anterior fascicular block in 1 patient in the eculizumab group.

Consequently, the analysis based on the SAP version 3.0 failed to demonstrate the superiority of eculizumab to placebo in patients with refractory gMG, but showed a trend toward increased improvement in MG symptoms in the eculizumab group, as compared with the placebo group. The primary analysis prespecified in the protocol and the SAP version 1.0 demonstrated the superiority of eculizumab to placebo. Accordingly, applicant explained that eculizumab is expected to have efficacy in the treatment of gMG with no major safety concerns.

7.2 Long-term extension study (CTD 5.3.5.2.1 and 5.3.5.2.3, Study ECU-MG-302, ongoing since November 2014 [data cutoff, [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted in patients who had completed the global phase III study (Study ECU-MG-301) to evaluate the long-term safety, efficacy, and pharmacokinetics of eculizumab (target sample size: approximately 92 patients) [for pharmacokinetics, see Section 6.2 Clinical pharmacology].

In the introduction phase, all patients received intravenous doses of the study drug in a blinded fashion weekly for 4 times (Weeks 0 [2 weeks after the last dose in Study ECU-MG-301], 1, 2, and 3), depending on the treatment assigned in Study ECU-MG-301. Patients randomized to eculizumab in Study ECU-MG-301 (the eculizumab/eculizumab group) received eculizumab 1200 mg at Weeks 0 and 2, and placebo at Weeks 1 and 3; patients randomized to placebo in Study ECU-MG-301 (the placebo/eculizumab group) received eculizumab 900 mg at Weeks 1 to 4. In the maintenance phase (from Week 4 onward), all patients received intravenous doses of eculizumab 1200 mg every 2 weeks. The maximum duration of treatment was 4 years.

All 117 patients treated (61 in the placebo/eculizumab group, 56 in the eculizumab/eculizumab group) were included in the safety analysis set. Of these 117 patients, 116 (60, 56) were included in the FAS as the efficacy analysis set, excluding 1 patient[7)] in the placebo/eculizumab group. In the safety analysis set, 13 patients (6, 7) discontinued the study. The major reasons for discontinuation were withdrawal of consent in 8 patients (5, 3) and adverse events in 2 patients (1, 1).

Changes in MG-ADL total score, which was the primary efficacy endpoint, are presented in Table 6.

Table 6. Changes in MG-ADL total score (FAS, OC)

	Placebo/eculizumab			Eculizumab/eculizumab		
	n	Total score	Change	n	Total score	Change
Baseline (Study ECU-MG-301)	60	9.9 ± 2.60		56	10.3 ± 3.03	
Week 1	60	6.0 ± 3.85	-3.9 ± 3.75	55	5.3 ± 3.94	-5.0 ± 4.07
Week 4	60	5.1 ± 3.74	-4.8 ± 3.73	55	5.5 ± 3.81	-4.9 ± 4.05
Week 12	60	5.2 ± 3.25	-4.7 ± 3.39	53	5.3 ± 3.50	-4.8 ± 3.38
Week 26	55	4.7 ± 3.20	-4.9 ± 3.20	49	5.1 ± 3.77	-5.2 ± 3.77
Week 40	31	3.8 ± 2.76	-5.7 ± 3.55	29	5.2 ± 4.22	-5.1 ± 4.65
Week 52	20	4.3 ± 3.06	-5.3 ± 3.24	20	5.8 ± 3.75	-4.4 ± 3.53
Final assessment (LOCF)	60	5.2 ± 3.97	-4.7 ± 4.24	56	6.1 ± 4.36	-4.3 ± 4.11

Mean ± SD

Adverse events (including laboratory abnormalities) occurred in 90.2% (55 of 61) of patients in the placebo/eculizumab group and 92.9% (52 of 56) of patients in the eculizumab/eculizumab group. One patient in the eculizumab/eculizumab group died (hepatic failure), and a causal relationship to eculizumab could not be ruled out.[8)] Serious adverse events other than death reported in the study are summarized in Table 7.

7) One patient enrolled in Sweden was excluded from the interim efficacy analysis because the Swedish regulatory authority did not approve the protocol amendment that allowed for the interim analysis.

8) Cytomegalovirus (CMV) associated hemophagocytic lymphohistiocytosis was confirmed by autopsy. Serious adverse events were disseminated intravascular coagulation, cytomegalovirus infection, pyrexia, histiocytosis haematophagic, and sepsis. A causal relationship to eculizumab could not be ruled out for all serious events.

Table 7. Serious adverse events other than death reported in Study ECU-MG-302

Placebo/eculizumab	Myasthenia gravis in 5 patients,[a)] haematoma/pulmonary congestion/respiratory failure/acute myocardial infarction/acute respiratory failure/rhabdomyolysis/pneumonia/anaemia, myasthenia gravis/skin papilloma/asthenia/urinary tract infection, gastroenteritis/upper respiratory tract infection/headache/muscular weakness, syncope/dehydration/metabolic encephalopathy, myasthenia gravis/loss of consciousness,[*] myasthenia gravis[*]/gastroenteritis,[*] calculus ureteric,[*] spinal compression fracture, tonsillitis,[*] headache,[*] malignant melanoma in situ,[*] prostate cancer,[*] pulmonary embolism,[*] and colon cancer in 1 patient each (19 patients in total)
Eculizumab/eculizumab	Myasthenia gravis,[*] pneumonia[*]/respiratory syncytial virus infection,[*] myasthenia gravis[*]/sepsis[*]/neuroendocrine carcinoma,[*] myasthenia gravis/myasthenia gravis crisis, myasthenia gravis[*]/small intestinal obstruction,[*] influenza/gastrointestinal haemorrhage, pseudomonal sepsis[*]/acute renal failure,[*] myocardial infarction, intervertebral disc protrusion, atrial fibrillation,[*] ovarian cyst, carotid artery stenosis, myasthenia gravis, intestinal obstruction, dyspepsia, bronchitis,[*] and, influenza[*] in 1 patient each (16 patients in total)

[*] Events for which a causal relationship to the study drug could not be ruled out
[a)] A causal relationship to the study drug could not be ruled out in 1 patient.

The incidences of adverse events (including laboratory abnormalities) for which a causal relationship to the study drug could not be ruled out were 49.2% (30 of 61 patients) in the placebo/eculizumab group and 62.5% (35 of 56 patients) in the eculizumab/eculizumab group. The major events were headache (9 patients in the placebo/eculizumab group, 5 patients in the eculizumab/eculizumab group), diarrhoea (5, 5), upper respiratory tract infection (3, 6), nasopharyngitis (4, 4), infusion related reaction (6, 1), pain in extremity (3, 4), myasthenia gravis (3, 4), and urinary tract infection (2, 4).

No clinically important changes in vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) or electrocardiogram were reported.

Accordingly, the applicant explained that long-term treatment with eculizumab will raise no significant safety concerns, and the efficacy of eculizumab will be sustained in patients with refractory gMG.

7.R Outline of the review conducted by PMDA

7.R.1 Analytical procedures in the global phase III study (CTD 5.3.5.1.1, Study ECU-MG-301)

PMDA asked the applicant to explain the reasons why the SAP was revised with the modified primary analysis method before unblinding in the global phase III study (CTD 5.3.5.1.1, Study ECU-MG-301).

The applicant's explanation:
Presuming that patients with gMG would need rescue therapy for worsened symptoms, a rank-based primary analysis was planned so that the efficacy of eculizumab would be evaluated based on the change in MG-ADL total score, the primary endpoint, with the implementation of rescue therapy taken into consideration. At the beginning of the study, the protocol specified a Worst-Rank analysis. In this analysis, to adjust the effect of rescue therapy, patients receiving rescue therapy were ranked in the ascending order of time to rescue therapy from shortest to longest time, and other patients were ranked in the descending order of the change from baseline in MG-ADL total score at Week 26 from most to least improvement. Subsequently, the primary analysis method was further discussed as detailed below in response to FDA’s comments, the SAP was amended before unblinding.

- Regarding the primary analysis defined in the protocol and the SAP version 1.0, FDA pointed out that[9)] [redacted]. The point raised by FDA was discussed, and the SAP was revised with an additional sensitivity analysis in patients withdrawn from the study without receiving rescue therapy despite meeting the criteria.[9)] These patients were ranked in the ascending order of time to meeting the criteria for rescue therapy from shortest to longest time, as with patients receiving rescue therapy (SAP version 2.0).
- FDA made the 2 comments on the SAP version 2.0 as mentioned in (a) and (b) below, and in response the SAP was revised after discussion. As a result, in the SAP version 3.0, based on the recognition that death and MG crisis were more serious than other events, ranking was performed with the highest priority given to patients who had died and the second highest to those who had experienced MG crisis over patients receiving rescue therapy or those withdrawn from the study, in the ascending order of time to the event. In addition, patients withdrawn from the study, regardless of whether the criteria for rescue therapy were met, were combined with patients receiving rescue therapy and ranked in the ascending order of time to the event, to evaluate the efficacy of eculizumab more conservatively. The revised SAP allowed for these changes made in the primary analysis (SAP version 3.0).
  (a) In the criteria for rescue therapy,[9)] equivalence between the criterion (i) (MG crisis) and criterion (ii) (worsening in MG-ADL score) is unclear. The applicant should clearly give the reason to assure bias-free evaluation, for example, among patients judged to be eligible for rescue therapy in the late stage of the study based on a high degree of seriousness of condition and patients judged to be eligible for rescue therapy in the early stage of the study based on a lower degree of seriousness. Use of sensitivity analyses should be considered as needed.
  (b) Patients receiving rescue therapy and patients withdrawn from the study without receiving rescue therapy should be ranked on the same scale in the primary analysis and sensitivity analysis.

PMDA's view:

The primary analysis should have been designed with careful discussion before initiating the study. When a major change occurs in the features of analysis, not only the SAP but also the protocol should be revised. The analysis based on the SAP version 3.0 failed to demonstrate the superiority of eculizumab to placebo (Table 4). PMDA asked the applicant to give the reason why the results of the primary analysis based on the protocol and the SAP version 1.0 (Table 3) differed from those based on the SAP version 3.0, and to explain their view on the clinically sound way of patient ranking with outcome of gMG, etc. taken into account.

The applicant's explanation:

The handling of patients who had died, experienced MG crisis, or withdrawn from the study differed between the primary analysis defined in the protocol and the SAP version 1.0 and that defined in the SAP version 3.0. Because of no deaths and only 1 patient in the eculizumab group experiencing MG crisis in Study ECU-MG-301, the handling of patients who had withdrawn from the study may have affected the results of the primary

9) Rescue therapy with IVIG or plasmapheresis was permitted for patients who met one of the following clinical deterioration criteria: (i) MG crisis; (ii) worsening to Grade 3 or by ≥2 points on any one of the MG-ADL individual items, excluding double vision and eyelid droop; and, (iii) the treating physician considers that the patient's health is in jeopardy if rescue therapy is not given.

analysis. Of the 8 patients withdrawn from the study (2 in the placebo group, 6 in the eculizumab group), 1 patient who had been falsely randomized and received no study drug was excluded, and the remaining 7 patients (2 in the placebo group, 5 in the eculizumab group) were closely investigated. The results indicated that 3 patients (2 in the placebo group, 1 in the eculizumab group) experienced worsening of MG symptoms and received rescue therapy after study discontinuation, 1 patient in the eculizumab group experienced worsening of MG symptoms and received no rescue therapy after study discontinuation despite meeting the rescue therapy criteria[9)] and 3 patients in the eculizumab group discontinued the study due to adverse events, with no worsening of MG symptoms after the start of treatment with the study drug.

It is considered clinically appropriate that patients who had died or experienced MG crisis were ranked worst because their condition was presumably more serious. However, patients receiving rescue therapy were combined with patients who had withdrawn from the study, regardless of whether the criteria for rescue therapy[9)] were met, to be ranked in the ascending order of time to the event according to the SAP version 3.0. This approach was clinically inappropriate because of possible bias in the evaluation of 3 patients who discontinued the study despite improved MG symptoms. Patients receiving rescue therapy and patients withdrawn from the study should be ranked in the same manner for other patient populations, after imputation for the missing MG-ADL total score.

Based on the above investigations, the modified SAP version 2.0[10)] was prepared after the SAP version 3.0, which incorporated a Worst-Rank analysis accounting for ranking of the clinical events of death, MG crisis, and rescue therapy/study discontinuation in patients eligible for rescue therapy, to analyze the change from baseline in MG-ADL total score and the clinical events at Week 26 in the FAS (Table 8). The Worst-Rank analysis achieved a statistically significant difference between the eculizumab group and the placebo group (*P* = 0.0160, Worst-Rank ANCOVA defined in the SAP modified version 2.0).

Table 8. Changes from baseline in MG-ADL total score at Week 26 (FAS, LOCF)

	MG-ADL total score[a)]			Clinical events[b)]		Worst-Rank analysis[c)]	
	Baseline	Week 26	Change	MG crisis	Rescue therapy or study discontinuation[d)]	Rank[e)]	Difference between the groups[f)]
Placebo	9.9 ± 2.64 (51) 9.0 (5, 18)	7.0 ± 3.36 (51) 6.0 (2, 16)	-2.8 ± 3.07 (51) -2.0 (-8, 7)	0	62.2 ± 55.40 (12) 43.5 (7, 178)	70.2 ± 4.41 (63)	-15.4 [-27.80, -2.92] *P* = 0.0160
Eculizumab	10.2 ± 2.98 (55) 10.0 (5, 18)	5.6 ± 4.02 (55) 5.0 (0, 15)	-4.7 ± 4.23 (55) -4.5 (-15, 4)	127.0 (1) 127 (127, 127)	80.7 ± 76.64 (6) 58.0 (1, 174)	54.8 ± 4.46 (62)	

a) Top, mean ± SD (n); bottom, median (minimum, maximum); in a population comprising patients who experienced no MG crisis, required no rescue therapy, and completed the 26-week treatment with the study drug, and patients who discontinued the study and did not meet any of the criteria for rescue therapy
b) Time to the event (days); top, mean ± SD (n); bottom, median (minimum, maximum)
c) Worst-Rank analysis, defined as the primary analysis in the SAP modified version 2.0[10)]
d) A population comprising patients who discontinued the study and met any of the criteria for rescue therapy
e) Adjusted mean ± SD of the rank[10)] (based on ANCOVA) (n)
f) Top, difference between the treatment groups; middle, 95% confidence interval for the difference between the groups; bottom, *P* value for comparison of the treatment groups

10) ANCOVA model in which patients were ranked in ascending order according to the following the priorities from (a) to (d), and the obtained rank was included as a response variable, treatment group and MGFA class as factors, and the MG-ADL total score at baseline as a covariate: (a) patients who died by Week 26 (ranked in ascending order of the number of days to death), (b) patients who experienced MG crisis (ranked in ascending order of the number of days to MG crisis), (c) patients who received rescue therapy, or those who discontinued the study and met the criteria for rescue therapy (ranked in ascending order of the number of days to rescue therapy or study discontinuation, whichever came first, if both events occurred), and (d) patients who received no rescue therapy, or those who discontinued the study and did not meet the criteria for rescue therapy (ranked in ascending order of the improvement from baseline in MG-ADL total score at Week 26 [LOCF])

PMDA's view:
The ranking method used in the primary analysis specified at the planning of Study ECU-MG-301 in the protocol and SAP version 1.0 was inappropriate for the following reasons: (a) the seriousness, etc. of events was not taken into account, and (b) patients who discontinued the study due to worsening of MG symptoms without receiving no rescue therapy and patients who completed the study were statistically lumped together. The disease condition or worsening of MG symptoms during the study should have been taken into consideration in designing the ranking method used in the primary analysis. The SAP version 3.0 that had been developed in consideration of the worsening of MG symptoms before unblinding during Study ECU-MG-301 failed to demonstrate the superiority of eculizumab to placebo, and thus failed to verify the efficacy of eculizumab. On the other hand, the Worst-Rank analysis designed after unblinding in Study ECU-MG-301 (SAP modified version 2.0) incorporated clinically appropriate ranking while taking into account of the above (a) and (b), as well as the outcomes in individual patients. Therefore, the results of the Worst-Rank analysis (SAP modified version 2.0) should also be taken into account in the evaluation of efficacy of eculizumab, although it is a post-hoc analysis. Eculizumab is expected to have efficacy in the treatment of gMG, because (i) the change in MG-ADL total score based on the Worst-Rank analysis (SAP modified version 2.0) and the clinical event-based ranking, although exploratory, showed a statistically significant difference between the eculizumab group and the placebo group, (ii) the primary analysis specified in the protocol and the SAP version 1.0 did not necessarily provide a clinically appropriate ranking but showed a statistically significant difference between the eculizumab group and the placebo group, and (iii) the primary analysis designed taking the worsening of MG symptoms into consideration before unblinding in Study ECU-MG-301 and specified in the SAP version 3.0 was likely to underestimate the efficacy of eculizumab, due to the conservative handling of patients who discontinued the study due to adverse events despite improved MG symptoms. Nevertheless, it is necessary to continue to collect data on the efficacy of eculizumab after market launch, because the efficacy of eculizumab could not be demonstrated in Study ECU-MG-301 and the number of Japanese patients randomized to the eculizumab group was very limited (3 patients) in the study [see Section 7.R.2 Evaluations in the global phase III study].

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

7.R.2 Evaluations in the global phase III study (CTD 5.3.5.1.1, Study ECU-MG-301)

7.R.2.1 Intrinsic and extrinsic ethnic factors

PMDA asked the applicant to explain how the intrinsic and extrinsic ethnic factors that may affect the efficacy or safety of eculizumab were considered in conducting the global phase III study (CTD 5.3.5.1.1, Study ECU-MG-301).

The applicant's explanation:
The impact of intrinsic and extrinsic ethnic factors on the efficacy or safety of eculizumab was considered to be small for the following reasons. The implementation of the phase III study of eculizumab as a global study was appropriate.

- Eculizumab is a humanized monoclonal antibody and no ethnic differences in the pharmacokinetics of eculizumab have been demonstrated for the approved indications (PNH and aHUS). This suggests that the pharmacokinetics of eculizumab does not differ greatly between the Japanese population and non-Japanese population.
- The diagnosis of MG has been made based on symptoms (e.g., eyelid ptosis, dysphagia, limb muscle weakness, respiratory disorder), pathogenic autoantibodies (e.g., anti-AChR antibodies, anti-MuSK antibodies), and NMJ dysfunction (e.g., edrophonium chloride test, electromyogram) both in and outside Japan (*Clin Exp Neuroimmunol.* 2015;6:21-31; *J Clin Invest.* 2006;116:2843-54).
- In Japan, the prevalence of MG is 118 per million people, with the ocular type accounting for 35.7% of the patients and the generalized type 64.3%. Of these patients, 13.3% have a history of MG crisis (*J Neurol Sci.* 2011;305:97-102). An epidemiologic study in Europe revealed that the prevalence of MG is from 131 to 278 per million people (e.g., *Eur J Neurol.* 2010;17:1445-50; *J Intern Med.* 2015;277:594-604) with the generalized type accounting for 75% to 90% of the patients (*J Clin Invest.* 2006;116:2843-54, *N Engl J Med.* 2016;375:2570-81), and 15% to 20% of these patients have a history of MG crisis *(Neurology.* 1997;48:1253-60, *J Neurol Sci.* 2007;261:127-33). These data indicate that the epidemiology of MG, including prevalence, disease type, and the incidence of MG crisis in Japan is similar to that overseas.
- In Japan, the standard MG treatment is immunotherapy, with the supportive use of cholinesterase inhibitors (e.g., pyridostigmine bromide, ambenonium chloride). In immunotherapy, oral corticosteroids are recommended as the first-line therapy, calcineurin inhibitors (cyclosporine, tacrolimus hydrate) as the second-line therapy, and IVIG and plasmapheresis as the third-line therapy (*Japanese Clinical Guidelines for Myasthenia Gravis 2014*. Nankodo Co., Ltd., 2014). Outside Japan, although approved drugs are not the same as in Japan, immunotherapy including oral corticosteroids are recommended for the treatment of MG, and IVIG and plasmapheresis are other treatment options for patients who do not respond to immunotherapy (*Neurology.* 2016;87:419-25). Both in and outside Japan, cholinesterase inhibitors, despite slightly different positioning of these drugs between the regions, are used in an early stage. Overall, there are no substantial differences in medications for gMG in Japan and other regions.

7.R.2.2 Differences in the efficacy and safety of eculizumab between countries/regions in the global phase III study

PMDA asked the applicant to explain the differences in the efficacy and safety of eculizumab among the countries/regions in Study ECU-MG-301.

The applicant's explanation:

As compared to the entire study population, many Japanese patients enrolled in Study ECU-MG-301 tended to have low body weight. Other tendencies of the Japanese patients were to have refractory gMG confirmed due to “failing to response to ≥2 immunosuppressive drugs for ≥1 year” and to have a history of hospitalization for MG within 2 years.

At the same time, the analysis results of MG-ADL total score[4)] and clinical events by country/region presented in Table 9 revealed that too many Japanese patients were incidentally randomized to the placebo group and, as a result, only 3 Japanese patients were randomized to the eculizumab group, precluding an adequate assessment of consistency between the Japanese patients and the entire study population. The MG-ADL total score in the placebo group improved greater in the Japanese patients than in the entire study population; however, the improvement in the Japanese patients were within the score distribution of the entire study population. MG-ADL total score is assessed by a physician based on patients' self-reports, and thus it may have yielded an accidentally high placebo effect. The changes from baseline in the MG-ADL total score at Week 26 in the 3 Japanese patients randomized to eculizumab (baseline, Week 26) were 1 (12, 13), −3 (15, 12), and −2 (10, 8); thus, MG symptoms improved from pre-treatment in 2 of these 3 patients. In the placebo/eculizumab group of the long-term extension study (CTD 5.3.5.2.1 and 5.3.5.2.3, Study ECU-MG-302), the changes in MG-ADL total score (mean ± SD) from baseline to Week 3 during the blind treatment phase were −4.8 ± 3.55 in the entire study population (60 patients) and −7.6 ± 2.72 in the Japanese patients (8 patients), suggesting certain improvement in the Japanese patients. Consequently, none of available data suggest a possible significant gap in the efficacy of eculizumab between the entire study population and the Japanese patients. Therefore, the efficacy of eculizumab in Japanese patients with refractory gMG may be evaluated based on the results from the entire study population of Study ECU-MG-301.

Table 9. MG-ADL total scores and clinical events by country/region in Study ECU-MG-301

	Treatment group	MG-ADL total score[a]			Clinical events[b]		Worst-Rank analysis[c]	
		Baseline	Week 26	Change	MG crisis	Rescue therapy or study discontinuation[d]	Rank[e]	Difference between the groups [95% CI]
Entire study population	Placebo	9.9 ± 2.64 (51) 9.0 (5, 18)	7.0 ± 3.36 (51) 6.0 (2, 16)	-2.8 ± 3.07 (51) -2.0 (-8, 7)	-	62.2 ± 55.40 (12) 43.5 (7, 178)	70.2 ± 4.41 (63)	-15.4 [-27.80, -2.92]
	Eculizumab	10.2 ± 2.98 (55) 10.0 (5, 18)	5.6 ± 4.02 (55) 5.0 (0, 15)	-4.7 ± 4.23 (55) -4.5 (-15, 4)	127.0 (1) 127.0 (127, 127)	80.7 ± 76.64 (6) 58.0 (1, 174)	54.8 ± 4.46 (62)	
Japan	Placebo	11.0 ± 2.83 (6) 10.5 (8, 16)	5.7 ± 2.58 (6) 5.5 (2, 9)	-5.3 ± 2.42 (6) -5.0 (-8, -2)	-	27.0 ± 5.66 (2) 27 (23, 31)	58.2 ± 41.45 (8) 51 (14, 119.5)	20.5 [-31.6, 72.6]
	Eculizumab	12.5 ± 3.54 (2) 12.5 (10, 15)	10.0 ±2.83 (2) 10 (8, 12)	-2.5 ±0.71 (2) -2.5 (-3, -2)	-	171 (1) 171 (171, 171)	78.7 ± 26.57 (3) 67.5 (59.5, 109)	
Asia-Pacific	Placebo	10.3 ± 2.99 (4) 10.0 (7, 14)	7.0 ± 4.16 (4) 7.0 (2, 12)	-3.3 ± 4.03 (4) -3.0 (-8, 1)	-	140.0 (1) 140.0 (140, 140)	68.5 ± 40.48 (5) 79.5 (14.0, 110.0)	-
	Eculizumab	-	-	-	-	-	-	
Europe	Placebo	9.6 ± 1.73 (12) 9 (7, 13)	7.4 ± 2.97 (12) 6.5 (4, 15)	-2.2 ± 2.48 (12) -2 (-7, 2)	-	71 ± 67.69 (6) 45 (7, 178)	83.8 ± 30.00 (18) 79.5 (22.5, 123.0)	-23.7 [-43.8, -3.6]
	Eculizumab	9.9 ± 2.89 (28) 9.5 (6, 18)	5.4 ± 4.01 (28) 5.5 (0, 14)	-4.5 ± 4.73 (28) -4 (-15, 4)	127.0 (1) 127.0 (127, 127)	72.8 ± 76.41 (4) 58.0 (1, 174)	59.6 ± 40.51 (33) 51 (1.0, 125.0)	
North America	Placebo	10 ± 2.97 (22) 9.5 (5, 18)	7.9 ± 3.62 (22) 7.0 (4, 16)	-2.1 ± 3.12 (22) -2 (-7, 7)	-	42.0 ± 17.35 (3) 46.0 (23, 57)	72.3 ± 27.94 (25) 79.5 (22.5, 119.5)	-29.9 [-49.3, -10.5]
	Eculizumab	10.9 ± 3.01 (20) 10.5 (5, 16)	5.1 ± 3.92 (20) 4.5 (0, 15)	-5.8 ± 3.86 (20) -7 (-12, 0)	-	22 (1) 22.0 (22, 22)	42.4 ± 35.76 (21) 22.5 (3.5, 121.0)	
South America	Placebo	9.0 ± 2.89 (7) 8.0 (6, 14)	5.0 ± 2.89 (7) 6.0 (2, 10)	-4.0 ± 3.11 (7) -5.0 (-8, 0)	-	-	51.4 ± 30.56 (7) 40.0 (14.0, 91.5)	9.7 [-29.2, 48.6]
	Eculizumab	8.2 ± 2.68 (5) 7 (6, 12)	5.2 ± 4.87 (5) 6 (0, 12)	-3.0 ± 2.83 (5) -4.0 (-6, 0)	-	-	61.1 ± 28.60 (5) 51.0 (31.5, 91.5)	

a) Top, mean ± SD (n); bottom, median (minimum, maximum); the results of patients who experienced no MG crisis or required no rescue therapy before the completion of the 26-week treatment with the study drug and patients who discontinued the study and did not meet any of the criteria for rescue therapy
b) Time (days) to the event; top, mean ± SD (n); bottom, median (minimum, maximum)
c) Worst-Rank analysis, defined as the primary analysis in SAP modified version 2.0[10]
d) The group of patients who discontinued the study and met any of the criteria for rescue therapy
e) Adjusted mean ± SD of the rank[10] (based on ANCOVA) (n)

Major adverse events in Japanese patients and non-Japanese patients in Studies ECU-MG-301 and ECU-MG-302 are presented in Table 10. Although in the small number of subjects, there were no adverse events specific to Japanese patients. It is therefore considered possible to evaluate the safety of eculizumab in Japanese patients with refractory gMG based on the results from the entire study population of Studies ECU-MG-301 and ECU-MG-302.

Table 10. Common adverse events in Japanese or non-Japanese patients in Studies ECU-MG-301 and ECU-MG-302

	Study ECU-MG-301						Study ECU-MG-302		
	Entire study population		Japanese		Non-Japanese		Entire study population (Eculizumab)	Japanese (Eculizumab)	Non-Japanese (Eculizumab)
	Placebo	Eculizumab	Placebo	Eculizumab	Placebo	Eculizumab			
N	63	62	8	3	55	59	117	11	106
All adverse events	56 (88.9)	53 (85.5)	7 (87.5)	2 (66.7)	49 (89.1)	51 (86.4)	107 (91.5)	11 (100)	96 (90.6)
Serious adverse events	18 (28.6)	9 (14.5)	2 (25.0)	1 (33.3)	16 (29.1)	8 (13.6)	35 (29.9)	4 (36.4)	31 (29.2)
Adverse events leading to study discontinuation	0	4 (6.5)	0	0	0	4 (6.8)	3 (2.6)	0	3 (2.8)
Major adverse events									
Headache	12 (19.0)	10 (16.1)	0	2 (66.7)	12 (21.8)	8 (13.6)	31 (26.5)	3 (27.3)	28 (26.4)
Nasopharyngitis	10 (15.9)	9 (14.5)	3 (37.5)	1 (33.3)	7 (12.7)	8 (13.6)	28 (23.9)	9 (81.8)	19 (17.9)
Myasthenia gravis	11 (17.5)	6 (9.7)	2 (25.0)	1 (33.3)	9 (16.4)	5 (8.5)	17 (14.5)	2 (18.2)	15 (14.2)
Upper respiratory tract infection	12 (19.0)	10 (16.1)	0	0	12 (21.8)	10 (16.9)	13 (11.1)	0	13 (12.3)
Nausea	9 (14.3)	8 (12.9)	0	0	9 (16.4)	8 (13.6)	12 (10.3)	1 (9.1)	11 (10.4)
Diarrhoea	8 (12.7)	8 (12.9)	0	0	8 (14.5)	8 (13.6)	17 (14.5)	1 (9.1)	16 (15.1)
Back pain	6 (9.5)	5 (8.1)	2 (25.0)	0	4 (7.3)	5 (8.5)	9 (7.7)	2 (18.2)	7 (6.6)
Dizziness	5 (7.9)	5 (8.1)	0	0	5 (9.1)	5 (8.5)	5 (4.3)	0	5 (4.7)
Myalgia	2 (3.2)	5 (8.1)	0	0	2 (3.6)	5 (8.5)	11 (9.4)	3 (27.3)	8 (7.5)
Contusion	2 (3.2)	5 (8.1)	0	0	2 (3.6)	5 (8.5)	6 (5.1)	1 (9.1)	5 (4.7)
Oral herpes	0	5 (8.1)	0	0	0	5 (8.5)	2 (1.7)	0	2 (1.9)
Urinary tract infection	5 (7.9)	4 (6.5)	1 (12.5)	0	4 (7.3)	4 (6.8)	8 (6.8)	0	8 (7.5)
Peripheral oedema	2 (3.2)	4 (6.5)	1 (12.5)	0	1 (1.8)	4 (6.8)	5 (4.3)	1 (9.1)	4 (3.8)
Pain in extremity	2 (3.2)	4 (6.5)	0	0	2 (3.6)	4 (6.8)	12 (10.3)	1 (9.1)	11 (10.4)
Pyrexia	2 (3.2)	4 (6.5)	0	0	2 (3.6)	4 (6.8)	6 (5.1)	0	6 (5.7)

n (%)

The results of Studies ECU-MG-301 and ECU-MG-301 suggested no possible substantial differences in the efficacy or safety of eculizumab in the treatment of refractory gMG among countries/regions. Therefore, it is possible to evaluate the efficacy and safety of eculizumab in Japanese patients with refractory gMG based on the results from the entire study populations of the global studies.

PMDA's view:

Study ECU-MG-301 revealed a significant imbalance between the treatment groups in the countries/regions of origin of the patients randomized, and the Japanese patients randomized to eculizumab was as few as 3. Therefore, it is difficult to adequately assess the consistency in efficacy and safety between Japanese patients and the entire patient population based on the results of the study. Study participants should have been randomized more carefully in a way that allows verify the appropriateness of the implementation of Study ECU-MG-301 as a global study and the consistency between Japanese patients and the entire patient population by, for example, using countries/regions as an assignment factor. Nevertheless, the change from baseline in MG-ADL total score by Week 3 of the blind treatment phase in the placebo/eculizumab group of Study ECU-MG-302 and the occurrence of adverse events in Studies ECU-MG-301 and ECU-MG-302 suggesting no tendencies to differ substantially between the Japanese patients and the entire study population. In addition, the use of eculizumab is limited for refractory MG that is a serious rare disease [see Section 7.R.5 Clinical positioning]. For these reasons, an additional confirmatory study to verify the efficacy and safety of eculizumab in Japanese patients may not be necessary. The efficacy and safety of eculizumab in Japanese patients with refractory gMG may be evaluated based on the results from the entire study populations of Studies ECU-MG-301 and ECU-MG-302, provided that relevant investigations are continued in patients with refractory gMG in the post-marketing setting. This conclusion will be finalized, taking account of comments from the Expert Discussion.

7.R.3 Efficacy

7.R.3.1 Efficacy endpoints in the global phase III study (CTD 5.3.5.1.1, Study ECU-MG-301)

PMDA asked the applicant to explain the reliability and appropriateness of the MG-ADL total score,[4)] which was the primary efficacy endpoint of the global phase III study (CTD 5.3.5.1.1, Study ECU-MG-301) and to justify the selection of the MG-ADL total score as the primary efficacy endpoint.

The applicant's explanation:

MG-ADL total score[4)] is a patient-reported measure of functional impairment relating to daily activities, and its reliability and appropriateness has been proven overseas (*Neurology.* 1999;52:1487-9; *Muscle Nerve.* 2011;44:727-31). Although its Japanese version has not yet been validated for reliability or appropriateness, MG-ADL total score serves as the appropriate primary efficacy endpoint of Study ECU-MG-301 for the following reasons: (a) it is a scoring system with only 4 grades, which definitions are clear enough to be distinguished from each other, and the Japanese translation of the simple English definitions is easy for patients to understand, allowing evaluation of the same quality in and outside Japan; (b) evaluators were trained to maintain consistency in the evaluation among them; and, (c) the score has been used in a Japanese clinical study of tacrolimus hydrate (*Curr Med Res Opin.* 2004;20:1269-73; *J Clin Neurosci.* 2006;13:39-44).

The secondary efficacy endpoints of Study ECU-MG-301 were Quantitative Myasthenia Gravis Score for Disease Severity (QMG) total score[11)] and Myasthenia Gravis Quality of Life 15-item Scale (MG-QoL15) total score[12)] assessing quality of life based on MG symptoms and physical and functional impairment. The changes from baseline in QMG total score and MG-QoL15 total score at Week 26 are presented in Table 11. The results indicate improvement in the eculizumab group as with MG-ADL total score. Thus MG symptoms were considered to have been appropriately assessed based on the MG-ADL total score.

11) A scoring measure assessing muscle weakness and fatigability, based on the results of quantitative examinations, in which the following 13 items are assessed on a 4-grade scale comprising Grades 0 (normal) to 3 (severe): double vision and eyelid ptosis (ocular muscles), facial muscle strength (facial muscles), swallowing of 4 oz. water and speech following counting aloud from 1 to 50 (bulbar symptoms), right hand grip, left hand grip, right arm outstretched, left arm outstretched, right leg outstretched, and left leg outstretched (gross motor), head lifted (axial muscles), and forced vital capacity (respiratory muscles)

12) A patient-reported measure assessing the impairment of daily life due to MG symptoms, in which the following 15 items are assessed on a 5-point scale, where 0 represents "not at all" and 4 represents "very much": mood (3 items), vision (1 item), eating (1 item), speech (1 item), grooming (1 item), moving (3 items), family needs (1 item), and social activities (4 items)

Table 11. Changes from baseline in QMG total score and MG-QoL15 total score at Week 26 (FAS, LOCF)

	Score[a)]			Clinical events[b)]		Worst-Rank analysis[c)]	
	Baseline	Week 26[d)]	Change[d)]	MG crisis	Rescue therapy and study discontinuation[e)]	Rank[f)]	Difference between the groups [95% CI]
QMG total score							
Placebo	16.4 ± 5.76 (51) 15.0 (8, 34)	14.1 ± 5.40 (51) 13.0 (5, 32)	-2.4 ± 3.70 (51) -3.0 (-11, 8)	-	62.2 ± 55.4 (12) 43.5 (7, 178)	71.6 ± 4.42 (63)	-17.7 [-30.14, -5.32]
Eculizumab	17.2 ± 5.02 (55) 17.0 (6, 31)	12.1 ± 5.97 (55) 12.0 (1, 27)	-5.2 ± 4.79 (55) -5.0 (-16, 2)	127.0 (1) 127.0 (127, 127)	80.7 ± 76.64 (6) 58.0 (1, 174)	53.9 ± 4.46 (62)	
MG-QoL total score							
Placebo	30.2 ± 13.10 (51) 30.0 (6, 60)	23.7 ± 13.38 (51) 20.0 (3, 58)	-6.5 ± 9.40 (51) -6.0 (-30, 16)	-	62.2 ± 55.4 (12) 43.5 (7, 178)	70.6 ± 4.48 (63)	-16.0 [-28.62, -3.37]
Eculizumab	32.0 ± 11.86 (55) 32.0 (6, 59)	19.1 ± 14.88 (55) 17.0 (0, 59)	-12.9 ± 13.94 (55) -10.0 (-44, 19)	127.0 (1) 127.0 (127, 127)	80.7 ± 76.64 (6) 58.0 (1, 174)	54.6 ± 4.52 (62)	

a) Top, mean ± SD (n); bottom, median (minimum, maximum)
b) Time to the event (days); top, mean ± SD (n); bottom, median (minimum, maximum)
c) Worst-Rank analysis, defined as the primary analysis in the SAP modified version 2.0[10)]
d) In patients who completed the 26-week treatment with the study drug without experiencing MG crisis and requiring no rescue therapy, and patients who discontinued the study and met none of the criteria for rescue therapy
e) In patients who discontinued the study and met any of the criteria for rescue therapy
f) Adjusted mean ± SD of the rank[10)] (based on ANCOVA) (n)

PMDA accepted the applicant's explanation and concluded that there were no substantial problems with the selection of MG-ADL total score as the primary efficacy endpoint of Study ECU-MG-301, and that MG symptoms were appropriately assessed based on MG-ADL total score.

7.R.3.2 Factors that affect the efficacy of eculizumab

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

The applicant's explanation:

Table 12 shows the results of patient characteristics-based subgroup analyses for the change from baseline in the MG-ADL total score in Study ECU-MG-301. The difference between the eculizumab group and the placebo group tended to be small in patients with no previous thymectomy. However, this is considered to be an accidental result due to a small sample size of the analysis. In Study ECU-MG-302, the changes (mean ± SD) from baseline in MG-ADL total score at Week 26 in patients with a previous thymectomy were −4.8 ± 3.21 in the placebo/eculizumab group (n = 25) and −5.3 ± 4.11 in the eculizumab/eculizumab group (n = 29), while those in patients with no previous thymectomy were −5.0 ± 3.25 in the placebo/eculizumab group (n = 30) and −5.2 ± 3.30 in the eculizumab/eculizumab group (n = 20), suggesting that a previous thymectomy is unlikely to affect the efficacy of eculizumab.

Table 12. Changes from baseline in MG-ADL total score at Week 26 by patient characteristics (FAS, LOCF[a])

		Change from baseline		Difference between the groups [95% CI][b]
		Placebo	Eculizumab	
Entire study population		-2.6 ± 0.48 (63)	-4.0 ± 0.48 (62)	-1.4 [-2.77, -0.07]
Age[c]	<46 years	-2.4 ± 0.70 (30)	-4.9 ± 0.69 (32)	-2.5 [-4.45, -0.51]
	≥46 years	-2.7 ± 0.65 (33)	-3.1 ± 0.69 (30)	-0.4 [-2.27, 1.54]
Sex	Male	-2.0 ± 0.73 (22)	-2.3 ± 0.75 (21)	-0.3 [-2.41, 1.86]
	Female	-2.9 ± 0.60 (41)	-4.8 ± 0.60 (41)	-2.0 [-3.65, -0.26]
Body weight[c]	<80.7 kg	-2.2 ± 0.72 (30)	-3.4 ± 0.69 (32)	-1.2 [-3.24, 0.75]
	≥80.7 kg	-3.0 ± 0.65 (33)	-4.5 ± 0.68 (30)	-1.4 [-3.33, 0.49]
Age at diagnosis[c]	<32.6 years	-2.4 ± 0.68 (31)	-4.2 ± 0.68 (31)	-1.8 [-3.73, 0.11]
	≥32.6 years	-2.9 ± 0.69 (32)	-3.8 ± 0.71 (31)	-0.9 [-2.90, 1.11]
Disease duration[c]	<6.9 years	-3.1 ± 0.63 (32)	-3.9 ± 0.68 (28)	-0.8 [-2.67, 1.05]
	≥6.9 years	-2.0 ± 0.71 (31)	-4.1 ± 0.68 (34)	-2.1 [-4.06, -0.14]
MGFA class	IIa or IIIa	-2.3 ± 0.63 (32)	-3.3 ± 0.66 (30)	-1.0 [-2.89, 0.79]
	IVa	-1.1 ± 4.21 (2)	-2.2 ± 2.77 (4)	-1.2 [-18.63, 16.30]
	IIb or IIIb	-3.2 ± 0.73 (26)	-4.7 ± 0.75 (25)	-1.5 [-3.56, 0.65]
	IVb	-0.1 ± 3.54 (3)	-6.9 ± 3.54 (3)	-6.8 [-22.88, 9.24]
MG-ADL total score at baseline[c]	<10	-1.4 ± 0.61 (32)	-3.8 ± 0.70 (24)	-2.4 [-4.32, -0.55]
	≥10	-3.5 ± 0.74 (31)	-4.4 ± 0.67 (38)	-0.9 [-2.88, 1.14]
Criterion for refractory type	Footnote 3(i)[d]	-3.0 ± 0.60 (41)	-3.4 ± 0.61 (42)	-0.4 [-2.11, 1.29]
	Footnote 3(ii)[e]	-1.7 ± 0.78 (22)	-5.1 ± 0.83 (20)	-3.4 [-5.75, -1.09]
Previous thymectomy	With	-2.1 ± 0.69 (31)	-4.7 ± 0.63 (37)	-2.6 [-4.48, -0.75]
	Without	-3.0 ± 0.69 (32)	-3.0 ± 0.77 (25)	-0.0 [-2.09, 2.06]

Adjusted mean ± SD (n)

a) Missing data for the MG-ADL total score at Week 26 were imputed using the Last Observation Carried Forward (LOCF) approach in patients requiring no rescue therapy, and using the last data obtained just before the rescue therapy in patients receiving rescue therapy.

b) Based on an ANCOVA including treatment group and MGFA class as factors, and the MG-ADL total score at baseline as a covariate

c) Stratified by median

d) "No response to ≥2 immunosuppressive therapies for ≥1 year "

e) "No response to ≥1 immunosuppressive therapy, experiencing ≥1 plasmapheresis or IVIG every 3 months regularly over the previous 12 months and requiring to continue with either therapy for the management of muscle weakness"

PMDA asked the applicant to explain the impact of concomitant drugs for gMG on the efficacy of eculizumab.

The applicant's explanation:

The results of subgroup analyses regarding the change from baseline in MG-ADL total score with or without concomitant drugs in Study ECU-MG-301 are presented in Table 13. Within each subgroup, there was no clear difference between the placebo group and the eculizumab group, suggesting that the efficacy of eculizumab is unlikely to be affected by the concomitant drugs.

Table 13. Changes from baseline in MG-ADL total score at Week 26 by concomitant drug (FAS, LOCF[a])

		Change from baseline		Difference between the groups [95% CI][b]
		Placebo	Eculizumab	
Entire study population		-2.6 ± 0.48 (63)	-4.0 ± 0.48 (62)	-1.4 [-2.77, -0.07]
Oral corticosteroids	With	-2.3 ± 0.56 (51)	-3.6 ± 0.57 (47)	-1.2 [-2.84, 0.36]
	Without	-3.8 ± 1.06 (12)	-5.3 ± 0.95 (15)	-1.5 [-4.66, 1.59]
Immunosuppressants other than oral corticoshoteroids[c]	With	-2.9 ± 0.52 (53)	-4.0 ± 0.50 (57)	-1.1 [-2.48, 0.36]
	Without	-1.3 ± 1.34 (10)	-5.1 ± 2.02 (5)	-3.8 [-9.19, 1.49]
Cholinesterase inhibitors	With	-2.6 ± 0.53 (53)	-4.1 ± 0.51 (58)	-1.5 [-3.00, -0.09]
	Without	-2.5 ± 1.05 (10)	-3.3 ± 1.71 (4)	-0.8 [-5.32, 3.65]

Adjusted mean ± SD (n)

a) Missing data for the MG-ADL total score at Week 26 were imputed using the LOCF approach in patients requiring no rescue therapy, and using the last data obtained just before the rescue therapy in patients receiving rescue therapy.

b) Based on an ANCOVA including treatment group and MGFA class as factors, and the MG-ADL total score at baseline as a covariate

c) Azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus hydrate, cyclophosphamide, and methotrexate

PMDA accepted the applicant's explanation, but also considers it necessary to continue to collect information on the possible influential factors on the efficacy of eculizumab (including the type of concomitant drugs) in the post-marketing setting.

Based on the above review, PMDA concluded that there are no particular problems with the efficacy of eculizumab.

7.R.4 Safety

7.R.4.1 Differences in safety profile between refractory gMG and the previously approved indications

PMDA asked the applicant to explain the differences in the safety profile of eculizumab between refractory gMG and the approved indications (PNH, aHUS).

The applicant's explanation:

Major adverse events reported from the clinical studies conducted in patients with gMG,[13] PNH,[14] or aHUS[15] are presented in Table 14. There were no adverse events that were reported specifically or more frequently in patients with gMG, as compared to those with PNH or aHUS, except MG, their underlying disease, frequently reported from patients with gMG, suggesting no substantial differences in the safety profile of eculizumab for gMG and the approved indications (PNH, aHUS).

Table 14. Major adverse events in clinical studies in patients with gMG, PNH, or aHUS

	gMG		PNH		aHUS
	Placebo	Eculizumab	Placebo	Eculizumab	(Eculizumab)
N	63	123	44	195	37
All adverse events	56 (88.9)	116 (94.3)	40 (90.9)	194 (99.5)	37 (100.0)
Serious adverse events	13 (20.6)	33 (26.8)	9 (20.5)	75 (38.5)	30 (81.1)
Common adverse events					
Headache	12 (19.0)	39 (31.7)	12 (27.3)	109 (55.9)	18 (48.6)
Nasopharyngitis	10 (15.9)	32 (26.0)	8 (18.2)	97 (49.7)	15 (40.5)
Diarrhoea	8 (12.7)	21 (17.1)	5 (11.4)	66 (33.8)	18 (48.6)
Myasthenia gravis	11 (17.5)	20 (16.3)	0	0	0
Nausea	9 (14.3)	19 (15.4)	5 (11.4)	63 (32.3)	15 (40.5)
Upper respiratory tract infection	12 (19.0)	18 (14.6)	10 (22.7)	80 (41.0)	13 (35.1)
Pain in extremity	2 (3.2)	16 (13.0)	1 (2.3)	39 (20.0)	5 (13.5)
Arthralgia	3 (4.8)	15 (12.2)	4 (9.1)	43 (22.1)	4 (10.8)
Back pain	6 (9.5)	14 (11.4)	4 (9.1)	49 (25.1)	9 (24.3)
Urinary tract infection	5 (7.9)	12 (9.8)	4 (9.1)	33 (16.9)	9 (24.3)
Cough	3 (4.8)	11 (8.9)	4 (9.1)	39 (20.0)	11 (29.7)
Pyrexia	2 (3.2)	10 (8.1)	2 (4.5)	40 (20.5)	11 (29.7)
Dizziness	5 (7.9)	10 (8.1)	5 (11.4)	39 (20.0)	6 (16.2)
Vomiting	5 (7.9)	9 (7.3)	5 (11.4)	50 (25.6)	18 (48.6)
Oropharyngeal pain	3 (4.8)	9 (7.3)	4 (9.1)	42 (21.5)	6 (16.2)
Oedema peripheral	2 (3.2)	9 (7.3)	1 (2.3)	8 (4.1)	11 (29.7)
Anaemia	0	7 (5.7)	1 (2.3)	8 (4.1)	13 (35.1)
Abdominal pain	2 (3.2)	3 (2.4)	5 (11.4)	42 (21.5)	7 (18.9)
Renal impairment	0	0	0	4 (2.1)	8 (21.6)

n (%)

[13] A global phase III study (CTD 5.3.5.1.1, Study ECU-MG-301) and a long-term extension study (CTD 5.3.5.2.1 and CTD 5.3.5.2.3, Study ECU-MG-302)

[14] Study C04-001 (CTD 5.3.5.1.1 submitted at application for PNH), Study C02-001 (CTD 5.3.5.2.1 submitted at application for PNH), Study E02-001 (CTD 5.3.5.2.2 submitted at application for PNH), Study X03-001/X03-001A (CTD 5.3.5.2.3 submitted at application for PNH), Study C04-002 (CTD 5.3.5.2.4 submitted at application for PNH), Study E05-001 (CTD 5.3.5.2.5 submitted at application for PNH)

[15] Study C08-002A/B (CTD 5.3.5.1.1 submitted at application for aHUS) and Study C08-003A/B (CTD 5.3.5.1.2 submitted at application for aHUS)

PMDA accepted the applicant's explanation. However, most patients with gMG to be treated with eculizumab are presumed to receive immunosuppressants concomitantly [see Section 7.R.5 Clinical positioning]. Section "7.R.4.2 Infections" discusses risks of infections.

7.R.4.2 Infections

7.R.4.2.1 Meningococcal infection

Eculizumab inhibits C5 causing to increase the risk of meningococcal infection. Patients with PNH, aHUS, the approved indications, are required to have been immunized with a meningococcal vaccine prior to the first dose of eculizumab. A majority of patients with gMG, the intended population of eculizumab, are presumed to receive concomitant immunosuppressants [see Section 7.R.5 Clinical positioning]. PMDA asked the applicant to explain the possibility that the concomitant immunosuppressants reduce immunity acquired by meningococcal vaccination, posing an increased risk of meningococcal infection in patients with gMG.

The applicant's explanation:

- Complement-mediated bacteriolysis and opsonophagocytosis are known to play roll in the early defense mechanism against meningococcal infection (*Clin Microbiol Rev.* 2000;13:144-66). Eculizumab is an anti-C5 antibody, thus inhibits the activation of C5 to block the complement-mediated bacteriolysis against *Neisseria meningitidis (N. meningitidis)*. Accordingly, opsonophagocytosis is the primary defense against meningococcal infection in patients treated with eculizumab. The package insert advises that patients with PNH or aHUS should be immunized with a meningococcal vaccine at least 2 weeks prior to the first dose of eculizumab in the "Warning" and "Precautions for Indications" sections.
- A majority of patients with gMG to be treated with eculizumab are presumably receiving an immunotherapy (including drugs yet to be approved in Japan), such as a cell growth inhibitor (e.g., azathioprine), alkylating agent (e.g., cyclophosphamide), or calcineurin inhibitor (e.g., tacrolimus hydrate) in combination with an oral corticosteroid. Because these drugs inhibit the activation or clonal proliferation of T cells and B cells (*Clin Exp Immunol.* 2014;175:408-18), the immune response to the initial vaccination may be reduced. At the same time, in light of the seriousness of gMG, discontinuation of the immunotherapy to activate the immune system prior to meningococcal vaccination is not a practical approach.
- According to post-marketing safety information[16)] of Japanese and non-Japanese patients, 21 of 99 patients experiencing meningococcal infection-related adverse events were receiving concomitant immunosuppressants (corticosteroids, 17 patients; calcineurin inhibitors, 11 patients; and cell growth inhibitors, 3 patients [including patients receiving immunosuppressants of ≥2 categories]). However, a relationship between immunosuppressants and meningococcal infection has not been clarified.
- The global phase III study (CTD 5.3.5.1.1, Study ECU-MG-301) required patients with gMG to be immunized with meningococcal vaccines ≥2 weeks prior to the first dose of eculizumab[17)] as with

16) Japanese data, collected from 2373.5 patient-years for approximately 7 years since April 16, 2010; foreign data, collected from 29792.1 patient-years for approximately 10 years since April 2, 2007

17) Excluding patients who had already been vaccinated within the effective duration specified by the vaccine manufacturer and those who had been vaccinated according to current clinical/national guidelines

treatment for the approved indications. However, because the meningococcal antibody titer was not measured, what degree of immunity against meningococcus the patients with gMG had acquired by immunotherapeutic vaccination is unknown.

- While no meningococcal infection-related adverse events[18] were reported in the clinical studies in patients with gMG,[13] 0.3% (5 of 1728) of patients receiving eculizumab experienced adverse events in all clinical studies using eculizumab. A total of 99 patients experiencing meningococcal infection-related adverse events (60 patients with PNH, 29 patients with HUS, and 10 other patients) were identified by post-marketing safety data of Japanese and foreign patients.[16] However, no patients with gMG were included, because eculizumab was just approved overseas in August 2017 for the indication of gMG. These findings do not suggest a trend toward an increased risk of meningococcal infection due to eculizumab therapy.

PMDA's view:

According to the applicant's explanation, patients with gMG, who are to be treated with eculizumab, may not acquire adequate immunity by normal meningococcal vaccination. PMDA requested the applicant to discuss again and explain the risk management measures for meningococcal infection.

The applicant's explanation on the incidence of meningococcal infection during eculizumab therapy:

- Of the known 12 serogroups of *N. meningitidis*, serogroups A, B, C, W, X, and Y are the predominant causative strains of invasive meningococcal infection (*Infect Dis Ther*. 2016;5:89-112). In Japan, serogroup Y accounts for 42% of the causative serogroups, followed by serogroups C and X, each of which accounts for 18% (*Vaccine*. 2016;34:4068-71). In Japan, a meningococcal vaccine against serogroups A, C, W-135, and Y (Menactra intramuscular injection) is commercially available, while a meningococcal vaccine against serotype B is also available in Europe and the US. Among the 99 patients affected by meningococcal infection revealed by the Japanese and foreign post-marketing safety data,[16] the most predominant serogroup was B (23 patients), followed by Y (14 patients), C (9 patients), W-135 (6 patients), and others (47 patients).
- A certain number of patients immunized with meningococcal vaccines have been infected with serogroup C, W-135, or Y. Even after the approval of a vaccine against Serogroup B in Europe and the US in 2014, 7 patients have been reported to have infected with meningococcus of serogroup B. There have also been patients infected with meningococcus of serogroups against which no vaccines are currently available. Considering this situation, it is impossible to completely eliminate the risk of meningococcal infection by vaccination alone, in patients receiving eculizumab for gMG, as well as for the approved indications.
- Post-marketing safety data revealed deaths of 10 Japanese or non-Japanese patients from meningococcal infection,[16] with delayed start of antibiotic therapy noted in all cases. In addition to the importance of meningococcal vaccination, sufficient information on the risk of meningococcal infection should be communicated to healthcare providers and patients and their families.

[18] Events corresponding to the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs), including "meningococcal" and the PT "Waterhouse-Friderichsen syndrome"

The applicant's explanation about re-examination of the following matters in their risk management measures against meningococcal infection:

- **Revaccination:** Both the Clinical Practice Guideline for Vaccination of the Immunocompromised Host edited by The Infectious Diseases Society of America (*Clin Infect Dis.* 2014;58:309-18) and the Vaccination Guidelines by the Japanese Society for Infection Prevention and Control (*Japanese Journal of Infection Prevention and Control.* 2017;32(supply);S1-5) recommend that immunosuppressed patients should receive meningococcal vaccines via a 2-dose primary series (8 weeks apart), followed by an additional dose every 5 years to sustain immunity, despite of no supporting data. In the US[19)] and UK (Immunization against infectious disease. *The green book.* Wellington House, 2013), a similar 2-dose primary series vaccination followed by revaccination is recommended for all patients receiving eculizumab. Similarly, in Japan, it is considered appropriate to immunize patients with gMG receiving eculizumab with meningococcal vaccines via a 2-dose primary series (8 weeks apart), followed by an additional dose every 5 years to sustain immunity.
- **Monitoring of meningococcal antibody titer:** The antibody titer that is required to prevent meningococcal infection remains controversial (*Clin Microbiol Rev.* 1991; 4:359-95) and yet to be established. Therefore, it is not appropriate to advise that meningococcal antibody titer be measured prior to eculizumab therapy or after meningococcal vaccination to determine the necessity of revaccination or discontinuation of eculizumab therapy.
- **Continuous antibiotic prophylaxis:** In France, continuous antibiotic prophylaxis is recommended during eculizumab therapy. However, the reported rate of meningococcal infection in France (0.38 per 100 person-years) since 2007 was similar to that in the entire world (0.31 per 100 person-years). Thus, the significance of continuous antibiotic prophylaxis while on eculizumab therapy has not been clarified, and it is not appropriate to advise to consider continuous antibiotic prophylaxis.
- **Exclusion of meningococcal carriers from the intended population of eculizumab:** *N. meningitidis* colonies are also found in the pharynx of healthy individuals, with an estimated prevalence of *N. meningitidis* of 0.4% in the Japanese general population (*Japanese Journal of Infectious Diseases.* 2005;79:527-33). A relationship between the prevalence of *N. meningitidis* in the general population and the risk of meningococcal infection has not been clarified (*Lancet.* 1973;2:205; *Hum Vaccin Immunother.* 2012;8:1029-35), and it is unclear whether the onset of meningococcal infection would be prevented by assessing the carriage of *N. meningitidis* prior to eculizumab therapy. Therefore, it is not appropriate to withhold the administration of eculizumab to meningococcal carriers.

Consequently, the risk of meningococcal infection in patients with gMG, the intended population of eculizumab, is considered to be minimized by taking the following risk management measures: to make a recommendation for additional immunization with meningococcal vaccines according to the applicable guidelines in and outside Japan (as a 2-dose primary series [8 weeks apart] with an additional dose every 5 years to maintain immunity), even though the effectiveness or usefulness has not been proven, and to organize

19) General best practice guidelines for immunization: best practices guidance of the Advisory Committee on Immunization Practices (ACIP). (https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html (finally confirmed on October 6, 2017)

materials for information provision to urge healthcare providers and patients and their families to closely monitor the patient's condition after the administration of eculizumab, promptly detect a sign of infection, and initiate appropriate antibiotic therapy.

PMDA's view:
A majority of patients with refractory gMG, the intended population of eculizumab, are presumed to have been receiving multiple immunosuppressants and to have a decreased ability to acquire sufficient immunity by meningococcal vaccination. Adequate discussion on risk management measures against meningococcal infection in patients with gMG should have been made before conducting Study ECU-MG-301 so that the effectiveness and usefulness of such measures could have been assessed in the study.

Repeated vaccinations as a 2-dose primary series followed by an additional dose of meningococcal vaccines every 5 years is recommended both in Japanese and foreign guidelines for vaccination in immunocompromised patients and in the foreign guidelines for vaccination in patients on eculizumab therapy. Even though the effectiveness or usefulness of the recommended vaccination in patients with gMG has not been proven until now, the package insert should advise that patients receiving eculizumab for gMG or the approved indications undergo meningococcal vaccination.

On the other hand, the solely vaccination-oriented risk management of meningococcal infection has limitations, in light of the incidence of meningococcal infection in patients who have received eculizumab therapy. Therefore, the provision of adequate information to healthcare providers and patients and their families is necessary. Details of the initial signs of meningococcal infection should also be communicated to patients receiving eculizumab for gMG or the approved indications, and the patients should be instructed to contact their physician immediately if such initial signs appear.

The incidence of meningococcal infection, and the effectiveness and usefulness of the 2-dose primary series with additional doses of meningococcal vaccines should be adequately evaluated in the post-marketing setting. In addition, the assessment of risk factors and risk management measures against meningococcal infection should be continued, and new information should be promptly communicated to healthcare providers, if any.

The appropriateness of the risk management measures against meningococcal infection for patients with gMG and of the cautionary advice on meningococcal infection during eculizumab therapy will be finalized, taking account of comments from the Expert Discussion.

7.R.4.2.2 Infections with other encapsulated bacteria

Complement activation is also important in preventing infections with non-meningococcal encapsulated bacteria. PMDA asked the applicant to explain the risk of infections with non-meningococcal encapsulated bacteria due to eculizumab therapy.

The applicant's explanation:

The main defense mechanism against infection with *N. meningitidis* is terminal complement (e.g., C5)-mediated lysis via the formation of membrane attack complexes, while opsonophagocytosis by upstream components of the complement pathway (e.g., C3) plays an important role in protection against infection with *Streptococcus pneumoniae* (*S. pneumoniae*) or other encapsulated bacteria (*Clin Microbiol Rev.* 1991;4:359-95; *Infect Immun.* 2005;73:4245-52). In addition, the association of infection with encapsulated bacteria other than Neisseria (e.g., *S. pneumoniae*) with congenital C5-deficient patients has not been elucidated (*Clin Microbiol Rev.* 2010;23:740-80). Therefore, the impact of C5 inhibition by eculizumab on infection with non-meningococcal encapsulated bacteria is considered limited.

The incidences of infections with non-meningococcal encapsulated bacteria (i.e., *S. pneumoniae* and *Haemophilus influenzae*) (adverse events relating to encapsulated bacterial infections[20)]) in the clinical studies using eculizumab[13)] were 0% in the gMG studies,[13)] 0.5% (1 of 195 patients) in the eculizumab group of the PNH studies,[14)] and 2.7% (1 of 37 patients treated with eculizumab) in the aHUS studies.[15)] A total of 23 (0.715 cases per 1000 patient-years) adverse events related to encapsulated bacterial infections were reported in the Japanese and foreign post-marketing safety information,[16)] including 5 deaths (including 1 Japanese patient) that occurred in patients with risk factors for infections, such as the concomitant use of immunosuppressants, renal failure, dialysis, and aplastic anaemia. A causal relationship to eculizumab was unknown for all deaths.

These results suggest that infections with non-meningococcal encapsulated bacteria are unlikely to pose a clinically important problem in patients with gMG treated with eculizumab. The current package insert has cautionary notes on this matter, which are sufficient and require no additional ones.

PMDA's view:
The applicant's explanation is acceptable. However, information on infections with non-meningococcal encapsulated bacteria should be further collected in the post-marketing setting.

7.R.4.2.3 Other infections

PMDA asked the applicant to explain the risk of infections with non-encapsulated bacteria due to eculizumab therapy.

The applicant's explanation:
The major adverse events[21)] related to infections with non-encapsulated bacteria in the clinical studies in patients with gMG,[13)] PNH[14)] or aHUS[15)] are presented in Table 15. In patients with gMG, there was no substantial difference in the incidence of these adverse events between the placebo group and the eculizumab group. The incidences of adverse events or serious adverse events related to infections with non-encapsulated bacteria showed no tendency to increase in patients with gMG, as compared to patients treated for the previously approved indications (PNH and aHUS).

20) Events corresponding to the MedDRA PTs under the High-Level Terms (HLT) of "Haemophilus infections," the PTs including "pneumococcal", or the PT "Haemophilus influenzae type b immunisation"
21) Events coded under the MedDRA SOC "Infections and infestations," except for PTs related to infections with *N. meningitidis* or encapsulated bacteria

Table 15. Major adverse events related to infections with non-encapsulated bacteria in clinical studies in patients with gMG, PNH, or aHUS

	gMG			PNH		aHUS (Eculizumab)
	Placebo[a)]	Eculizumab[a)]	Eculizumab (pooled)[b)]	Placebo	Eculizumab	
N	63	62	123	44	195	37
Adverse events related to infections with non-encapsulated bacteria	36 (57.1)	41 (66.1)	89 (72.4)	31 (70.5)	181 (92.8)	34 (91.9)
Serious adverse events	6 (9.5)	2 (3.2)	14 (11.4)	4 (9.1)	31 (15.9)	13 (35.1)
Major adverse events						
Nasopharyngitis	10 (15.9)	9 (14.5)	32 (26.0)	8 (18.2)	97 (49.7)	15 (40.5)
Upper respiratory tract infection	12 (19.0)	10 (16.1)	18 (14.6)	10 (22.7)	80 (41.0)	13 (35.1)
Bronchitis	1 (1.6)	3 (4.8)	13 (10.6)	1 (2.3)	13 (6.7)	6 (16.2)
Urinary tract infection	5 (7.9)	4 (6.5)	12 (9.8)	4 (9.1)	33 (16.9)	9 (24.3)
Influenza	1 (1.6)	1 (1.6)	11 (8.9)	1 (2.3)	15 (7.7)	4 (10.8)
Gastroenteritis	1 (1.6)	0	8 (6.5)	2 (4.5)	19 (9.7)	6 (16.2)
Sinusitis	2 (3.2)	1 (1.6)	5 (4.1)	3 (6.8)	23 (11.8)	5 (13.5)
Viral infection	0	0	0	5 (11.4)	31 (15.9)	0

n (%)
a) The placebo group and the eculizumab group of Study ECU-MG-301
b) Pooled data from the eculizumab groups of Studies ECU-MG-301 and ECU-MG-302

During the clinical studies in patients with gMG,[13)] PNH,[14)] or aHUS,[15)] sepsis-related adverse events[22)] occurred in 2 of 62 patients in Study ECU-MG-301 (gMG), 2 of 123 patients in Study ECU-MG-302 (gMG), and 2 of 37 patients in the aHUS studies (all in the eculizumab groups). Of these, 1 patient in Study ECU-MG-302 died. Although a causal relationship between eculizumab and the death could not be ruled out, the use of concomitant immunosuppressants (corticosteroids and azathioprine) was a possible influential factor.

The association between congenital C5 deficiency and *Neisseria gonorrhoeae* (*N. gonorrhoeae*), a non-meningococcal Neisseria species, has been noted (*Clin Microbiol Rev.* 2010;23:740-80). In the clinical studies in patients with gMG,[13)] PNH,[14)] or aHUS,[15)] no gonococcal infection[23)] occurred. Japanese and foreign post-marketing safety data[16)] revealed gonococcal infection affected 9 patients (4 with gonococcal sepsis, 3 with disseminated gonococcal infection, and 1 each with bacteraemia due to *N. gonorrhoeae* and gonorrhoea). All these events resolved after appropriate antibiotic therapy.

These findings have suggested no new safety concerns regarding infection with non-encapsulated bacteria in patients with gMG receiving eculizumab. Therefore, no additional cautionary notes need to be given in the package insert.

PMDA accepted the applicant's explanation. However, more information on infections with non-encapsulated bacteria should be collected in the post-marketing setting.

PMDA concluded that there are no other particular problems with the safety of eculizumab.

7.R.5 Clinical positioning

22) Events coded under the MedDRA HLT "Sepsis, bacteraemia, viraemia, and fungaemia NEC"
23) Events coded under the MedDRA HLT "Neisseria infections," except for the PTs including "meningococcal" and the PT "Waterhouse-Friderichsen syndrome"; or, events corresponding to the PT "Neisseria test positive"

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

The applicant's explanation:
There are no Japanese or foreign guidelines stating the clinical positioning of eculizumab in the treatment of gMG. Given this fact, the applicant presented the following views:

- The Japanese clinical guidelines (*Japanese Clinical Guidelines for Myasthenia Gravis.* 2014, Nankodo Co., Ltd., 2014) place immunotherapy as the current standard treatment of gMG, recommending the supportive use of cholinesterase inhibitors (e.g., pyridostigmine bromide, ambenonium chloride). The first-line immunotherapy is with oral corticosteroids. The guidelines further recommend calcineurin inhibitors (tacrolimus hydrate, cyclosporine) as the second-line therapy for symptoms inadequately controlled by corticosteroids, and IVIG and plasmapheresis as the third-line therapy. Thymectomy is a treatment option to be considered for patients with gMG suffering concomitant thymoma or being anti-AChR antibody-positive. These treatments are recommended in foreign clinical guidelines as well, although there are some differences in the approval statuses of drugs from those in Japan (*Neurology.* 2016;87:419-25).
- Although treatment with corticosteroids and/or calcineurin inhibitors helps many patients achieve remission, approximately 10% of patients with gMG are refractory to such treatments and require IVIG or plasmapheresis (*BMC Neurol.* 2010;10:46-54; *J Clin Neuromuscul Dis.* 2014;15:167-78). IVIG and plasmapheresis, however, are effective only transiently, and the patients are required to undergo treatment on a regular basis for symptom control over the long term, which would be physically burdensome for the patients. Thus, there are unmet medical needs for eculizumab in the treatment of gMG.
- Eculizumab acts by the mechanism that differs from those of existing MG drugs [see Section 3.R.1 Mechanism of action of eculizumab] and is expected to be effective in patients refractory to the currently available treatment options. Eculizumab thus has been developed in the expectation that it be placed in a position similar to IVIG or plasmapheresis from a clinical point of view. Eculizumab may also have therapeutic effects when used alone as the first-line therapy, given its mechanism of action. However, the global phase III study (CTD 5.3.5.1-1, Study ECU-MG-301) was conducted in patients who were considered to require IVIG or plasmapheresis, based on the above-mentioned expectation.[2)] It is therefore difficult to explain the efficacy and risks or benefits of eculizumab in other patient populations based on the study data.
- As mentioned above, eculizumab has been developed to be used while being clinically positioned similarly to IVIG or plasmapheresis. The results of Study ECU-MG-301 in patients requiring IVIG or plasmapheresis showed the promising efficacy of eculizumab [see Section 7.R.2 Evaluations in the global phase III study] with no major safety concerns. Therefore, eculizumab should be similarly positioned to IVIG or plasmapheresis from the clinical viewpoint, and be used with either IVIG or plasmapheresis according to the condition of the patient and at the discretion of physicians.

PMDA's view:

In developing a drug with a novel mechanism of action, appropriate patient population should be selected based on the safety profile and risk-benefit balance of the drug. Limiting the target population by only focusing on the unmet medical needs for the drug is not always an appropriate approach, which will deprive others of opportunities to choose the treatment option. However, in the development of eculizumab, limiting the intended population to patients who were refractory to conventional treatments was appropriate, considering the known risk of eculizumab for fatal meningococcal infection. Therefore, it is acceptable to place eculizumab in a clinical position similar to that of IVIG or plasmapheresis.

On the other hand, the intended population of eculizumab is presumed to concomitantly use multiple immunosuppressants, and they are considered a high risk population that may have difficulty acquiring immunity via meningococcal vaccination. The effectiveness or usefulness of the risk management measures against meningococcal infection in the intended population has not been assessed in clinical studies and will need to be assessed in the post-marketing setting [see Section 7.R.4.2 Infections]. Given this situation, an alternative is to limit the use of eculizumab to patients who do not sufficiently respond to IVIG or plasmapheresis. Eculizumab will provide a new treatment option for the treatment of refractory gMG. However, its clinical positioning will be finalized after due examination of the risks and benefits of eculizumab, and taking account of comments from the Expert Discussion.

7.R.6 Indication and intended population

7.R.6.1 Indication

PMDA asked the applicant to explain the appropriateness of the proposed indication of eculizumab, in view of the clinical positioning of eculizumab.

The applicant's explanation:
Eculizumab is expected to be positioned similarly to IVIG or plasmapheresis for patients with refractory gMG from a clinical point of view [see Section 7.R.5 Clinical positioning]. While the Japanese clinical guidelines (Japanese Clinical Guidelines for Myasthenia Gravis 2014. Nankodo Co., Ltd., 2014) provide no clear definition of patients with refractory gMG, the international consensus guidance for management of MG, established by experts in Japan, the US, and Europe (*Neurology.* 2016;87:419-25) regards refractory MG as a condition in which the "post-intervention status remains unchanged or worsens with persistent symptoms or adverse reactions that limit functions, after corticosteroids and ≥2 other immunosuppressants are administered at an appropriate dose for an appropriate duration by the decisions of the patient and physician." Therefore, the indication of the drug should be defined as the treatment of "patients with refractory gMG." To make clear that the other immunosuppressants includes drugs used during the period from the diagnosis of gMG through just before starting eculizumab therapy, the clause to the effect that "who have inadequate response to existing therapies or are inadequately controlled with prior therapies" was added to the proposed indication.

In view of the intended population and clinical positioning of eculizumab that are the same as those of IVIG, however, the indication of eculizumab was reconsidered. The indication of eculizumab was then defined as follows, which is identical to that of IVIG:

Indication (proposed modification)
Generalized myasthenia gravis (only for patients inadequately responding to corticosteroids or non-corticosteroid immunosuppressants)

PMDA accepted the applicant's explanation. PMDA considers that there are no particular problems with the above indication (proposed modification), if eculizumab can be clinically positioned similarly to IVIG or plasmapheresis. This conclusion will be finalized taking account of comments from the Expert Discussion.

7.R.6.2 Administration to patients presenting with MG crisis

PMDA asked the applicant to explain the efficacy and safety of eculizumab when administered to patients presenting with MG crisis.

The applicant's explanation:
MG crisis is characterized by worsened respiratory or bulbar muscle weakness, causing respiratory failure requiring endotracheal intubation and ventilator management. Eculizumab may also be effective in patients presenting with MG crisis, given its mechanism of action [see Section 3.R.1 Mechanism of action of eculizumab].

Because of their unstable clinical condition, patients presenting with MG crisis were not considered suitable for the global phase III study involving placebo as the control (CTD 5.3.5.1.1, Study ECU-MG-301) and were excluded from the study. Therefore, no efficacy and safety data of eculizumab are available obtained from patients presenting with MG. The occurrence of MG crisis was reported in 1 patient in the eculizumab group of Study ECU-MG-301 and 1 patient in the long-term extension study (CTD 5.3.5.2.1, Study ECU-MG-302). A causal relationship to eculizumab is considered less likely in these patients for the following reasons: (a) both patients experienced an upper respiratory tract infection before presenting with MG crisis, and the MG crisis was considered to have been induced by the upper respiratory tract infection through complement activation (*Cell Res.* 2010;20:34-50); and (b) the patient in Study ECU-MG-302 experienced MG crisis 18 days after the latest dose of eculizumab (despite the dosage regimen specifying the every 2-week dosing), and the possibility cannot be denied that the longer dosing interval may have been an influential factor of MG crisis. Thus eculizumab is unlikely to have caused MG crisis. The patient experiencing MG crisis in Study ECU-MG-301 repeatedly underwent plasmapheresis and eculizumab therapy with no particular safety concerns.

Despite lack of systematic evaluation, eculizumab is also expected to be effective in patients presenting with MG crisis based on its mechanism of action, with no particular safety concerns identified. Therefore, no specific cautionary advice needs to be given in the package insert on the use of the drug in patients presenting with MG crisis.

PMDA's view:

The exclusion of patients with MG crisis from Study ECU-MG-301 was unavoidable for the appropriate evaluation of the efficacy and safety of eculizumab. Although few data are available on the efficacy of safety of eculizumab administered to patients with MG crisis, a specific caution on treating patients with MG crisis is considered unnecessary for the following reasons: (a) patients with MG crisis do not necessarily have to be excluded from the intended population of eculizumab in view of the pathological condition of MG crisis and the action mechanism of eculizumab, and (b) the discontinuation of eculizumab therapy in patients experiencing MG crisis during therapy is impractical in view of the clinical positioning of eculizumab. Healthcare professionals should be provided with written information about the lack of efficacy and safety data of eculizumab administered to patients with MG crisis. Efficacy and safety information of eculizumab should be gathered from patients experiencing MG crisis in the post-marketing setting.

7.R.6.3 Impacts of thymoma

PMDA asked the applicant to explain why patients have a history of thymoma and those who had undergone thymectomy within 12 months were excluded from Study ECU-MG-301 and the efficacy and safety of eculizumab in those populations.

The applicant's explanation:

The thymus is an important lymphoid tissue that eliminates T cells responding to autoantigens so that autoimmune tolerance is maintained. Early-onset MG that develops by around 50 years of age is often accompanied by follicular hyperplasia (55%), and late-onset MG developing after around 50 years of age may found with thymoma (23%) (*J Autoimmun.* 2014;52:90-100; *Clin Exp Neuroimmuno.* 2014;5:84-91). In some patients with MG, pathological changes in the thymus reduce immune tolerance, leading to the production of anti-AChR antibodies (*Clin Exp Neuroimmunol.* 2016;7:226-37). The Japanese clinical guidelines specify that thymectomy is indicated for all cases of thymoma and follicular hyperplasia in patients with early-onset MG (Japanese Clinical Guidelines for Myasthenia Gravis 2014. Nankodo Co., Ltd, 2014). Accordingly, patients with a history of thymoma and those with a history of thymectomy within 12 months were excluded from Study ECU-MG-301 for the following reasons so as to select patient population suitable for efficacy evaluation.

- Patients with a history of thymoma: Regardless of whether having a history of thymectomy, pathological condition of each patient may differ. A majority of these patients have severe MG, and some have another concomitant autoimmune disease.
- Patients with a history of thymectomy within 12 months: Many patients have decreased anti-AChR antibodies post-thymectomy (*J Autoimmun.* 2014;52:90-100). However, there is no consistency in the change, and the manifestation of the clinical effect of thymectomy may require time (*N Engl J Med.* 2016;375:511-22). In addition, patients in the immediate post-thymectomy phase are at risk of postoperative complications.

There are a certain proportion of patients not experiencing a decrease in anti-AChR antibodies after thymectomy, and patients with MG who are anti-ACR antibody-positive are known to have complement-binding IgG1 subclass antibodies, regardless of the presence or absence of thymoma (*Reptile Venoms and Toxins. Handbook of Natural Toxins, vol 5.* Marcel Dekker; 1991. p362-5). The use of eculizumab is limited to patients who are anti-AChR antibody-positive [see Section 3.R.1 Mechanism of action of eculizumab].

Therefore, eculizumab is expected to have a certain level of efficacy, regardless of whether patients have a history of thymoma or have undergone thymectomy.

In Study ECU-MG-301, the incidences of adverse events in patients with a previous thymectomy were 87.1% (27 of 31 patients) in the placebo group and 83.8% (31 of 37 patients) in the eculizumab group, and those in patients without a previous thymectomy were 90.6% (29 of 32 patients) in the placebo group and 88.0% (22 of 25 patients) in the eculizumab group, suggesting no safety concerns. Eculizumab suppresses the immune system, and the drug may be used in elderly patients, etc. who have thymoma unresected. Therefore, the possibility that thymoma may recur or worsen due to eculizumab therapy was assessed. An ongoing foreign prospective observational study[24)] has yielded the incidence rates of malignant tumors per 100 patient-years [95% confidence interval] of 1.38 [1.12, 1.69] in patients with PNH receiving eculizumab, 3.38 [2.92, 3.92] in those receiving no eculizumab, 0.22 [0.04, 0.63] in patients with aHUS receiving eculizumab, and 0.81 [0.22, 2.08] in those receiving no eculizumab, indicating no risk of progression of malignancies due to eculizumab therapy. Thus, eculizumab is unlikely to aggravate thymoma or increase the risk of recurrent malignancies in patients who underwent thymectomy for thymoma.

Based on the above, the efficacy or safety of eculizumab is less likely to be affected by a history of thymectomy or thymoma.

PMDA accepted the applicant's explanation. Patients with a history of thymoma need not be excluded from the patient population to be treated with eculizumab. However, post-marketing data on the impacts of a history of thymoma on the efficacy and safety of eculizumab should be gathered.

7.R.7 Dosage and administration

7.R.7.1 Rationale for the dosage and administration

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

The applicant's explanation:

The approved dosage regimen for PNH (600 mg weekly in the induction phase, 900 mg every 2 weeks in the maintenance phase) was found to not always provide adequate C5 inhibition. Hence, higher doses (900 mg weekly in the induction phase, 1200 mg every 2 weeks in the maintenance phase) were selected for the dosage regimen for aHUS (the review report at approval for aHUS). Eculizumab acts on C5 in the serum, and serum C5 concentration is not considered to differ greatly among patients with PNH, aHUS, and gMG. The dosage regimen for patients with gMG therefore could be determined based on that approved for PNH and aHUS.

24) A multi-center, global, non-interventional, prospective, observational study in patients with PNH (Study M07-001) or aHUS(Study M11-001), treated or not treated with eculizumab in prior clinical studies

The foreign phase II study in patients with gMG (CTD 5.3.5.1.3, Study C08-001)[25] followed the dosage regimen of that approved for PNH (600 mg weekly in the induction phase, 900 mg every 2 weeks in the maintenance phase). The results showed that ≥20% of C5 activity remained in 23% (3 of 13) of patients treated with eculizumab, indicating that higher doses would be required. Therefore, Study ECU-MG-301 employed the same dosage regimen as that for aHUS (900 mg in the induction phase, 1200 mg every 2 weeks in the maintenance phase). The results of the study showed that ≥20% of C5 activity remained in 13% (8 of 62) of patients in the eculizumab group, which was lower than that in Study C08-001. The MG-ADL total score suggested the efficacy of eculizumab, and the occurrence of adverse events did not differ significantly as compared to Study C08-001.

In view of these results, the proposed dosage and administration of eculizumab for the treatment of gMG is appropriate.

PMDA's view:
The applicant's explanation is acceptable, and there are no major problems with the proposed dosage and administration. However, the conclusion will be finalized taking account of comments from the Expert Discussion.

7.R.7.2 Discontinuation of eculizumab therapy

PMDA asked the applicant to explain whether the discontinuation of eculizumab therapy should be considered when, for instance, the patient achieves the remission of MG, in view of the clinical positioning of eculizumab [see Section 7.R.5 Clinical positioning] and the risk of meningococcal infection [see Section 7.R.4.2.1 Meningococcal infection].

The applicant's explanation:
Given the pathology of gMG and the current practice with IVIG and plasmapheresis, the discontinuation of eculizumab therapy should be considered in some cases including a remission sustained for a certain period of time. However, changes in QMC total score in 6 patients in the eculizumab/placebo group of Study C08-001 (Table 16) revealed that 2 patients who had achieved improvement by treatment with eculizumab and the condition was sustained even during the placebo treatment phase, while 3 patients experienced recurrence of symptoms during the placebo treatment phase. Thus, it is not always appropriate to decide to discontinue eculizumab therapy after a short interval from improvement.

[25] A placebo-controlled, randomized, cross-over, comparative study to evaluate the efficacy, safety, and pharmacokinetics of eculizumab in patients with refractory gMG who have moderate to severe muscle weakness despite prior treatment with immunosuppressants. The study was composed of treatment phase 1 (16 weeks), a washout period (5 weeks), treatment phase 2 (16 weeks), and a follow-up period (5 weeks). Patients received multiple intravenous doses of placebo or eculizumab (600 mg weekly, for a total of 4 doses at Weeks 0, 1, 2, and 3, followed by 900 mg every 2 weeks, for a total of 7 doses at Weeks 4 to 16) in each treatment phase.

Table 16. Changes in QMG total score in Study C08-001 (LOCF)

Patient ID	Baseline	Treatment phase 1 (Eculizumab)	Treatment phase 2 (Placebo)
[redacted]-001	16	8 (-8)	8 (-8)
[redacted]-002	18	18 (±0)	16 (-2)
[redacted]-002	20	8 (-12)	15 (-5)
[redacted]-003	26	15 (-11)	20 (-6)
[redacted]-002	17	14 (-3)	15 (-2)
[redacted]-001	26	11 (-15)	22 (-4)

QMG total score (change from baseline)

The results of Study ECU-MG-301 indicate that a certain proportion of patients fail to achieve adequate remission by eculizumab therapy, that patients with gMG treated with eculizumab are at an increased risk especially for meningococcal infection, and that about 3% of Japanese patients with gMG have C5 genetic polymorphisms with a markedly decreased binding activity of eculizumab for C5 [see Section 3.R.1 Mechanism of action of eculizumab]. Hence, patients who have failed to achieve adequate remission should be advised to discontinue eculizumab therapy. The appropriate timing to decide whether to discontinue eculizumab therapy is around 12 weeks after the start of therapy, because 25.6% (16 of 62) of patients were responded at Week 4 and 35.5% (22 of 62) at Week 12 in Study ECU-MG-301.[26)]

Accordingly, the duration of recurrence-free remission of gMG symptoms after the discontinuation of eculizumab may vary greatly by individual, and it is not appropriate to give advice on the discontinuation of long-term eculizumab therapy. On the other hand, healthcare professionals should be advised to consider the discontinuation of eculizumab therapy for patients who fail to respond to eculizumab by Week 12.

PMDA's view:
The applicant explained that no advice would be given in the package insert to encourage to consider the discontinuation of eculizumab therapy for patients achieving remission, and this is acceptable. However, 2 of the 6 patients in the eculizumab/placebo group of Study C08-001 had sustained remission after the discontinuation of eculizumab therapy, suggesting that there may be cases in which the therapy can be terminated. Considering the risk of meningococcal infection associated with eculizumab therapy [see Section 7.R.4.2.1 Meningococcal infection], patients should be treated with the minimum necessary doses of eculizumab. Some patients in Study C08-001 achieved sustained remission after the discontinuation of eculizumab therapy, and this should be properly communicated to healthcare professionals. Given the pharmacological effects of eculizumab, the available clinical data, and the risk of meningococcal infection associated with eculizumab, advising to consider the discontinuation of therapy is acceptable for patients failing to respond to eculizumab by Week 12 of the therapy.

7.R.8 Post-marketing investigations

PMDA's view:

26) Patients experiencing a reduction in MG-ADL total score of ≥3 points and a reduction in QMG total score of ≥3 points, and receiving no rescue therapy

Although the efficacy of eculizumab in the treatment of gMG is promising, Study ECU-MG-301 failed to clearly demonstrate the efficacy of eculizumab, and had as few as 3 Japanese subjects in the eculizumab group. Therefore, it is necessary to continue to collect information on the efficacy and safety of eculizumab in Japanese patients with gMG via the post-marketing surveillance. Based on the clinical study data and the Japanese and foreign post-marketing safety data, the post-marketing surveillance should be aimed to gather data of the incidence of meningococcal infection, the effectiveness and usefulness of meningococcal revaccinations administered as a 2-dose primary series with additional doses, the incidence of infection with non-meningococcal encapsulated bacteria, the incidence of infections with non-encapsulated bacteria, the efficacy and safety of eculizumab in patients with genetic polymorphisms that decrease binding activity of eculizumab and in patients with MG crisis, the impact of the history of thymoma on the efficacy and safety of eculizumab, the efficacy of eculizumab administered concomitantly with IVIG, and factors affecting the efficacy of eculizumab.

Because of the risks such as for meningococcal infection, eculizumab has previously been approved for PNH and aHUS with a condition, which requires necessary measures taken to ensure that eculizumab be administered only under the supervision of physicians with expertise in the diagnosis of PNH and aHUS at medical institutions capable of managing the risks etc. associated with eculizumab, and in cooperation with physicians with expertise in the diagnosis and treatment of meningococcal infection. On the understanding that appropriate risk mitigation measures have been taken, similar measures should be taken for patients with gMG as well.

The applicant's explanation:
A specified drug use-results survey will be performed covering all patients treated with eculizumab as the post-marketing surveillance for eculizumab, due to the limited clinical data from Japanese patients with gMG. As with the previously approved indications (PNH and aHUS), the risk mitigation measures will be taken for patients with gMG.

The PMDA's conclusion on the appropriateness of these actions proposed by the applicant will be finalized, taking account of comments from the Expert Discussion.

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

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

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

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

The new drug application data (CTD 5.3.5.1.1, 5.3.5.2.1, and 5.3.5.2.3) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The clinical studies had been generally conducted in compliance with GCP and PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted. During the inspection, however, PMDA identified the following finding requiring corrective action at the sponsor. The sponsor was notified of the finding, although it did not substantially affect the overall evaluation.

The finding requiring corrective action:

Sponsor

- Some information on serious, unexpected adverse drug reactions was not properly provided to the investigators and the heads of the study sites.

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

On the basis of the data submitted, PMDA has concluded that eculizumab has efficacy in the treatment of gMG, and that eculizumab has acceptable safety in view of the benefits with due risk management measures against meningococcal infection established. Eculizumab is clinically meaningful because it offers a new treatment option for patients with refractory gMG. The risk of meningococcal infection and the clinical positioning of eculizumab should be further reviewed at the Expert Discussion.

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

Review Report (2)

November 24, 2017

Product Submitted for Approval

Brand Name	Soliris for Intravenous Infusion 300 mg
Non-proprietary Name	Eculizumab (Genetical Recombination) (JAN)
Applicant	Alexion Pharma Godo Kaisha
Date of Application	March 22, 2017

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 in the following. 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 issues presented in Review Report (1).

PMDA additionally discussed the following points and took action as necessary.

1.1 Efficacy of eculizumab

1.1.1 Efficacy evaluation in the global phase III study

The expert advisors supported the following PMDA conclusions (1) and (2).

(1) For efficacy evaluation in the global phase III study (CTD 5.3.5.1.1, Study ECU-MG-301), the ranking method used in the primary analysis that was specified at the time of study planning (the protocol and the SAP version 1.0) was not necessarily appropriate from a clinical standpoint. The ranking method in the Worst-Rank analysis defined after unblinding in Study ECU-MG-301 (the SAP modified version 2.0) is considered more appropriate from a clinical standpoint [see Section 7.R.1 Analytical procedures in the global phase III study of the Review Report (1)].

(2) Eculizumab is expected to have efficacy in the treatment of gMG for the following reasons: (i) the Worst-Rank analysis (the SAP modified version 2.0) for the change in MG-ADL total score and the clinical events showed a statistically significant difference between the eculizumab group and the placebo group, although it was an exploratory assessment. (ii) The primary analysis defined in the protocol and the SAP version 1.0, although which was not necessarily clinically appropriate, showed a statistically significant difference between the eculizumab group and the placebo group. (iii) The primary analysis before unblinding in Study ECU-MG-301 and defined in the SAP version 3.0 was designed in consideration for worsening of MG symptoms. The

efficacy of eculizumab may have been underestimated due to conservative counting of patients experiencing adverse events leading to study discontinuation despite improved MG symptoms [see Section 7.R.1 Analytical procedures in the global phase III study of the Review Report (1)].

The expert advisors' comment:
Ranking-based efficacy evaluation yields different results depending on the analytical method employed and lacks stability, and the efficacy of eculizumab cannot be fully discussed based on such analysis alone. Changes in MG-ADL total score, etc. should also be taken into account. The changes in MG-ADL total score in Tables 3, 4, and 8 showed greater improvement in the eculizumab group than in the placebo group, supporting the above conclusion that eculizumab has promising efficacy in the treatment of gMG.

The expert advisors also supported the following PMDA conclusion.
Study ECU-MG-301 failed to clearly demonstrate the efficacy of eculizumab, and the number of Japanese patients assigned to the eculizumab group was as few as 3. Therefore, it is difficult to discuss the efficacy of eculizumab in Japanese patients with gMG based only on the results of the study, and it is necessary to adequately evaluate the efficacy of eculizumab via the post-marketing surveillance [see Section 7.R.1 Analytical procedures in the global phase III study of the Review Report (1)].

Based on the above review, PMDA instructed the applicant to take appropriate actions. The applicant agreed (see Table 21).

1.1.2 Efficacy by symptom

The expert advisors commented that the efficacy of eculizumab should also be carefully evaluated based on MG-ADL or QMG subscore relating to MG symptoms. In response, PMDA asked the applicant to present the results of the analyses by subscore and to explain the efficacy of eculizumab for each MG symptom.

The applicant's explanation:
Tables 17 and 18 show the changes from baseline in subscores of MG-ADL and QMG at Week 26 in Study ECU-MG-301. There was no substantial improvement in the MG-ADL bulbar subscore, while the QMG score, a tool for physicians to objectively assess MG symptoms, showed improvements in bulbar symptoms. For the other symptoms, either or both of the MG-ADL subscore or QMG subscore showed a trend toward a greater improvement in the eculizumab group than in the placebo group.

Table 17. Changes from baseline in MG-ADL subscores at Week 26 in Study ECU-MG-301 (FAS, LOCF)

	Placebo			Eculizumab		
	Baseline	Week 26	Change	Baseline	Week 26	Change
Ocular muscles[a)]	3.6 ± 1.61 (61) 4.0 (1, 6)	3.1 ± 1.90 (61) 3.0 (0, 6)	-0.5 ± 1.46 (61) 0.0 (-3, 4)	3.7 ± 1.48 (61) 4.0 (1, 6)	2.5 ± 2.04 (61) 2.0 (0, 6)	-1.3 ± 1.70 (61) -1.0 (-4, 4)
Gross motor or limb impairment[a)]	2.8 ±1.15 (57) 3.0 (1, 5)	2.1 ± 1.49 (57) 2.0 (0, 5)	-0.7 ± 1.45 (57) -1.0 (-3, 3)	2.9 ± 1.21 (58) 3.0 (1, 5)	1.7 ± 1.65 (58) 1.0 (0, 6)	-1.2 ±1.58 (58) -1.0 (-4, 1)
Respiratory muscles[a)]	1.2 ±0.42 (46) 1.0 (1, 2)	1.0 ±0.56 (46) 1.0 (0, 2)	-0.2 ± 0.55 (46) 0.0 (-1, 1)	1.3 ± 0.48 (54) 1.0 (1, 2)	0.8 ± 0.70 (54) 1.0 (0, 2)	-0.5 ±0.82 (54) 0.0 (-2, 1)
Bulbar symptoms[a)]	3.2 ± 1.37 (57) 3.0 (1, 6)	1.9 ± 1.58 (57) 2.0 (0, 6)	-1.3 ±1.80 (57) -1.0 (-6, 3)	3.1 ± 1.42 (60) 3.0 (1, 6)	1.7 ± 1.90 (60) 1.0 (0, 7)	-1.4 ± 1.82 (60) -1.0 (-6, 2)

Top, mean ± SD (n [patients requiring no rescue therapy]); bottom, median (minimum, maximum)
a) Ocular muscles (double vision, eyelid ptosis), bulbar symptoms (talking, chewing, swallowing), respiratory muscles (breathing), gross motor or limb impairment (impairment of ability to brush teeth or comb hair, impairment of ability to arise from a chair)

Table 18. Changes from baseline in QMG subscores at Week 26 in Study ECU-MG-301 (FAS, LOCF)

	Placebo			Eculizumab		
	Baseline	Week 26	Change	Baseline	Week 26	Change
Ocular muscles[a)]	3.7 ± 1.78 (63) 4.0 (0, 6)	3.3 ± 2.03 (63) 3.0 (0, 6)	-0.4 ± 1.21 (63) 0.0 (-3, 3)	3.5 ± 1.80 (62) 4.0 (0, 6)	2.6 ± 2.03 (62) 3.0 (0, 6)	-0.9 ± 1.87 (62) -1.0 (-6, 3)
Facial muscles[a)]	1.2 ± 0.83 (63) 1.0 (0, 3)	0.9 ± 0.90 (63) 1.0 (0, 3)	-0.3 ± 0.69 (63) -0.3 (-2, 2)	1.3 ± 0.88 (62) 1.0 (0, 3)	0.7 ± 0.87 (62) 0.0 (0, 3)	-0.6 ± 0.73 (62) -1.0 (-3, 1)
Bulbar symptoms[a)]	1.1 ± 1.35 (63) 0.0 (0, 5)	0.9 ± 1.48 (63) 0.0 (0, 6)	-0.1 ± 1.31 (63) 0.0 (-4, 4)	1.2 ± 1.52 (62) 1.0 (0, 6)	0.7 ± 1.29 (62) 0.0 (0, 6)	-0.5 ± 1.29 (62) 0.0 (-6, 2)
Gross motor[a)]	8.5 ± 3.20 (63) 8.0 (2, 18)	7.8 ± 3.43 (63) 8.0 (0, 17)	-0.7 ± 2.35 (63) -1.0 (-5, 4)	8.8 ± 2.96 (62) 9.0 (2, 16)	7.1 ± 3.60 (62) 8.0 (0, 16)	-1.7 ± 2.83 (62) -1.5 (-9, 6)
Axial muscles[a)]	1.5 ± 0.78 (63) 2.0 (0, 3)	1.4 ± 0.78 (63) 1.0 (0, 3)	-0.1 ± 0.61 (63) 0.0 (-1, 1)	1.7 ± 0.70 (62) 2.0 (0, 3)	1.3 ± 0.80 (62) 1.0 (0, 3)	-0.4 ± 0.73 (62) 0.0 (-2, 1)
Respiratory muscles[a)]	0.9 ± 0.95 (63) 1.0 (0, 3)	1.0 ± 1.00 (63) 1.0 (0, 3)	0.1 ± 0.76 (63) 0.0 (-1, 2)	0.8 ± 1.02 (62) 0.0 (0, 3)	0.7 ± 0.89 (62) 0.5 (0, 3)	-0.1 ± 0.70 (62) 0.0 (-2, 2)

Top, mean ± SD (n in patients requiring no rescue therapy); bottom, median (minimum, maximum)
a) Ocular muscles (double vision, eyelid ptosis), facial muscles (facial muscle strength), bulbar symptoms (swallowing of 4 oz. water and speech following counting aloud from 1 to 50), gross motor (right and left hand grip, arm outstretched, and leg outstretched), axial muscles (head lifted), respiratory muscles (forced vital capacity)

PMDA accepted the applicant's explanation.

1.2 Risk management of infections

1.2.1 Meningococcal infection

The expert advisors supported the following PMDA's conclusion regarding the risk management measures against meningococcal infection to be taken for patients treated with eculizumab: The foreign and Japanese clinical practice guidelines for vaccination in immunosuppressed patients and the foreign guidelines for vaccination in patients treated with eculizumab recommend that patients receiving eculizumab be immunized with meningococcal vaccines via a primary series of 2-doses followed by an additional dose every 5 years. It is thus appropriate that the package insert advises the importance of meningococcal revaccination for patients receiving eculizumab for gMG or the approved indications. Information on the frequency of vaccination should be provided through written materials because of no clear evidence [see Section 7.R.4.2.1 Meningococcal infection in the Review Report (1)]. The expert advisors also supported the following PMDA's conclusion: Vaccination has limited effect in preventing meningococcal infection. Initial signs of meningococcal infection should be communicated in detail to healthcare professionals, patients, and their families, and patients should be instructed to contact their physicians immediately once any initial sign occurs [see Section 7.R.4.2.1 Meningococcal infection of the Review Report (1)]. The expert advisors noted that some patients treated with eculizumab experienced sepsis due to meningococcal infection, without being accompanied by meningitis in some cases, and that the package insert should give cautionary advice about possible sepsis due to meningococcal infection for early detection of meningococcal infection.

Based on the above review, PMDA instructed the applicant to properly modify descriptions in the package insert and other information materials and to establish a system so that eculizumab be used appropriately for the treatment of gMG under the same approval conditions as those for the treatment of PNH or aHUS. The applicant agreed.

1.2.2 Other infections

The expert advisors commented that the risk of non-meningococcal infections, namely, infections with *N. gonorrhoeae* and *Haemophilus influenzae*, should be carefully assessed due to the increased susceptibility to infection by C5 inhibition, and that invasive *Haemophilus influenzae* infection, of which most of the causative agents are categorized into unencapsulated strains, have recently affected 300 people per year in Japan and may pose a risk as with meningococcal infection. According to Japanese and foreign post-marketing safety information,[16)] a total of 7 patients suffered from *Haemophilus influenzae* infection,[27)] with 1 of them suspected to be invasive, and 9 patients experienced gonococcal infection.[23)] The expert advisors commented that there are no clear safety concerns at present. As long as appropriate information is provided to healthcare professionals, active recommendation of *Haemophilus influenzae* vaccination is not necessary.

Based on the above review, PMDA instructed the applicant to properly modify the information materials concerning non-meningococcal infections. The applicant agreed.

1.3 Clinical positioning and indication of eculizumab

The expert advisors commented that eculizumab should be indicated only for patients with gMG whose symptoms are uncontrollable by IVIG or plasmapheresis, rather than placed in the same clinical position as IVIG or plasmapheresis, for the following reasons: (a) although the efficacy of eculizumab can be expected based on the results of Study ECU-MG-301, it has not yet been demonstrated; (b) a majority of patients with gMG, the intended population of eculizumab, use immunosuppressants and are therefore presumed to have increased risk of meningococcal infection, invasive *Haemophilus influenzae* infection, and other serious infections; and, (c) some patients experienced rapidly progressive meningococcal infection and had a fatal outcome.

Based on the above review, PMDA instructed the applicant to modify the indication of eculizumab as follows. The applicant agreed.

Indication (Only the part relevant to the current review)
Treatment of patients with generalized myasthenia gravis (only for symptoms uncontrollable with high-dose intravenous immunoglobulin therapy or plasmapheresis)

1.4 Risk management plan (draft)

27) Events corresponding to the MedDRA PTs under the HLT "Haemophilus infections" or the PT "Haemophilus influenzae type b immunisation"

In view of the discussions presented in Section "7.R.8 Post-marketing investigations" in the Review Report (1) and comments from the expert advisers at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for eculizumab should include the safety specification presented in Table 19, and that the applicant should implement the additional pharmacovigilance activities and risk minimization activities presented in Table 20.

Table 19. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Meningococcal infection (including sepsis) • Severe thrombotic microangiopathy due to the discontinuation of eculizumab therapy in patients with aHUS • Infusion reaction	• Serious haemolysis due to the discontinuation of eculizumab therapy in patients with PNH	• Not applicable
Efficacy specification		
• Not applicable		

Table 20. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities[a)]	Additional risk minimization activities[a)]
• Early post-marketing phase vigilance • Specified use-results survey	• Disseminate data gathered during the early post-marketing phase vigilance • Organize and disseminate materials for healthcare professionals • Organize and disseminate materials for patients

[a)] Only the additional pharmacovigilance activities and risk minimization activities relating to the present proposed indication are presented.

PMDA requested that the applicant conduct post-marketing surveillance to investigate the issues above.

The applicant explained that they will conduct the specified use-results survey for patients with gMG presented in Table 21.

Table 21. Outline of the specified use-results survey (draft)

Objective	To evaluate the safety and efficacy of eculizumab in clinical practice after market launch
Survey method	All-case surveillance
Population	Patients with gMG treated with eculizumab
Observation period	Up to 3 years (Patients withdrawn from eculizumab therapy will be followed up for 8 weeks)
Planned sample size	200 patients[a)]
Main survey items	• Patient characteristics (gender, age, severity, anti-AChR antibodies, history of thymoma and surgery (thymus), past history, complications, vaccination status, C5 gene polymorphisms, etc.) • Exposure to eculizumab (duration of treatment, dose, dosing frequency, changes in dosage regimen and the reasons) • Prior medications/therapies, concomitant medications/therapies • Adverse events • Causative agents (also serotype for *N. meningitis*) of infections, if any • Efficacy (e.g., MG-ADL total score, QMG total score) • Laboratory data, body weight

[a)] The planned sample size is based on the number of patients expected to participate in the survey (around 200 patients), as estimated from the number of patients with gMG in Japan and the intended population of eculizumab. The efficacy of eculizumab will be confirmed with the upper limit of the 95% confidence interval of the mean change from baseline in both MG-ADL total score and QMG total score of <–3. Assuming that the mean changes from baseline in the MG-ADL total score and QMG total score at Week 26 and their standard deviations are similar to those in Study ECU-MG-301 (–4.4 ± 4.34 and –5.0 ± 5.17), a sample size of ≥100 efficacy evaluable patients will provide a statistical power of ≥90%.

PMDA accepted the above survey plan and also considers that the results of the survey should be promptly

provided to healthcare professionals.

1.5 Current status of the ongoing global long-term extension study

PMDA asked the applicant to explain the updated occurrence of adverse events in the global long-term extension study (CTD 5.3.5.2.1 and 5.3.5.2.3, Study ECU-MG-302).

The applicant's explanation:

Adverse events resulting in death, collected since the cutoff date for the present application on [redacted], 20[redacted] up to [redacted], 20[redacted] were pneumonia aspiration in 1 patient and cardiogenic shock/pulmonary embolism/deep vein thrombosis in 1 patient. A causal relationship to eculizumab could not be ruled out for cardiogenic shock/pulmonary embolism/deep vein thrombosis. The serious adverse events other than death reported during this period are presented in Table 22. As compared with the serious adverse events reported in the clinical studies (Tables 5 and 7), no new safety concerns have been suggested.

Table 22.Serious adverse events other than death

Myasthenia gravis in 8 patients;[a)] pyrexia in 3 patients;[a)] anaemia, aspergillus infection,[a)] bronchitis,[a)] myelodysplastic syndrome, myositis, pneumonia aspiration, pulmonary embolism, and upper respiratory tract infection in 2 patients each; abdominal incarcerated hernia, acute renal failure, acute respiratory failure, asthenia, autoimmune disorder,[*] bursitis infective staphylococcal,[*] cardiogenic shock,[*] cellulitis,[*] chronic obstructive pulmonary disease, colon cancer, colonic abscess,[*] deep vein thrombosis, encephalopathy, fall,[*] gastritis, gastroenteritis,[*] gastrostomy tube site complication, haemoglobin decreased,[*] hospitalisation, hypoglycaemia, large intestine polyp, lymphoma, myasthenia gravis crisis, pain in extremity, pancreatitis acute, pneumonia,[*] procedural pain, pseudomonas infection, rectal abscess,[*] rib fracture, sepsis, urinary tract infection,[*] vaginal haemorrhage, vertigo positional, and wound infection in 1 patient each

[*] Events for which a causal relationship to eculizumab could not be ruled out
[a)] A causal relationship to eculizumab could not be ruled out in 2 patients

PMDA accepted the applicant's explanation and considers that no new concerns have arisen regarding the long-term safety of eculizumab.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indications and the dosage and administration as follows, with the conditions for approval shown below. As the product is an orphan drug, the re-examination period for the proposed additional indication is 10 years.

Indications

Reduction of hemolysis in patients with paroxysmal nocturnal hemoglobinuria
Inhibition of thrombotic microangiopathy in patients with atypical hemolytic uremic syndrome
Treatment of patients with generalized myasthenia gravis (only for symptoms uncontrollable with high-dose intravenous immunoglobulin therapy or plasmapheresis)

(Underline denotes additions.)

Dosage and Administration

Reduction of hemolysis in patients with paroxysmal nocturnal hemoglobinuria

The usual adult dosage is 600 mg as Eculizumab (Genetical Recombination) given as an intravenous infusion weekly for a total of 4 doses, followed 1 week later (4 weeks after the first dose) by 900 mg given every 2 weeks thereafter.

Inhibition of thrombotic microangiopathy in patients with atypical hemolytic uremic syndrome

Eculizumab (Genetical Recombination) is usually administered as an intravenous infusion according to the schedules below.

Age or body weight	Induction phase	Maintenance phase
≥18 years old	900 mg weekly × 4 doses	1200 mg every 2 weeks, from 4 weeks after the first dose
<18 years old		
≥40 kg	900 mg weekly × 4 doses	1200 mg every 2 weeks, from 4 weeks after the first dose
≥30 kg and <40 kg	600 mg weekly × 2 doses	900 mg every 2 weeks, from 2 weeks after the first dose
≥20 kg and <30 kg	600 mg weekly × 2 doses	600 mg every 2 weeks, from 2 weeks after the first dose
≥10 kg and <20 kg	600 mg weekly × 1 dose	300 mg every 2 weeks, from 1 week after the first dose
≥5 kg and <10 kg	300 mg weekly × 1 dose	300 mg every 3 weeks, from 1 week after the first dose

Treatment of patients with generalized myasthenia gravis (only for symptoms uncontrollable with high-dose intravenous immunoglobulin therapy or plasmapheresis)

The usual adult dosage is 900 mg of Eculizumab (Genetical Recombination), given as an intravenous infusion weekly for a total of 4 doses, followed 1 week later (4 weeks after the first dose) by 1200 mg given every 2 weeks thereafter.

(Underline denotes additions.)

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because data from Japanese clinical studies are limited, the applicant is required to conduct a use-results survey over a specified period, covering all patients treated with the product, to understand the characteristics of patients treated with the product and to obtain safety and efficacy data so as to take necessary measures for the product to be used properly.
3. The applicant is required to take necessary post-marketing measures so that the product is administered only under the supervision of physicians and at medical institutions with expertise in the diagnosis and treatment of generalized myasthenia gravis and capability for managing the risks, etc. of the product, and only in cooperation with physicians with expertise in the diagnosis and treatment of meningococcal infection.

List of Abbreviations

AChR	Acetylcholine Receptor
aHUS	Atypical Hemolytic Uremic Syndrome
CTD	Common Technical Document
DNA	Deoxyribonucleic Acid
ELISA	Enzyme-linked Immunosorbent Assay
FAS	Full Analysis Set
FDA	Food and Drug Administration
gMG	Generalized Myasthenia Gravis
HLT	High-Level Terms
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgG	Immunoglobulin G
IVIG	Intravenous Immunoglobulin
LOCF	Last Observation Carried Forward
Lrp4	Low-Density Lipoprotein Receptor-Related Protein 4
MedDRA	Medical Dictionary for Regulatory Activities
MG	Myasthenia Gravis
MG-ADL	Myasthenia Gravis-Activity of Daily Living Profile
MGFA	Myasthenia Gravis Foundation of America
MG-QoL	Myasthenia Gravis-Quality of Life
MuSK	Muscle-Specific Receptor Tyrosine Kinase
NEC	Not Elsewhere Classified
OC	Observed Case
PMDA	Pharmaceuticals and Medical Devices Agency
PNH	Paroxysmal Nocturnal Hemoglobinuria
PT	Preferred Term
QMG	Quantitative Myasthenia Gravis
SAP	Statistical Analysis Plan
SMQ	Standardised MedDRA Queries
SOC	System Organ Class
placebo/eculizumab group	Patients randomized to placebo in Study ECU-MG-301 and enrolled in Study ECU-MG-302
eculizumab/eculizumab group	Patients randomized to eculizumab in Study ECU-MG-301 and enrolled in Study ECU-MG-302