Report on the Deliberation Results

March 5, 2010

Evaluation and Licensing Division, Pharmaceutical and Food Safety 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 K.K.
[Date of application]	March 31, 2009

[Results of deliberation]
In the meeting held on February 26, 2010, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

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

[Conditions for approval]
1. Due to limited data from Japanese clinical studies, conduct a post-marketing drug use-results survey over a certain period of time, covering all patients treated with Soliris, in order to obtain the background information of patients treated with Soliris, collect data on the safety and efficacy of Soliris, and take necessary measures to ensure proper use of Soliris.
2. Prior to marketing Soliris, take necessary measures to ensure that Soliris will be administered only under the supervision of a physician at a medical institution, who is familiar with the diagnosis and treatment of paroxysmal nocturnal hemoglobinuria and is also fully capable of managing the risks etc. associated with Soliris, in cooperation with a physician who is familiar with the diagnosis and treatment of meningococcal infection.

**Japanese Accepted Name (modified INN)*

Review Report

February 18, 2010
Pharmaceuticals and Medical Devices Agency

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

[Brand name]	Soliris for Intravenous Infusion 300 mg (Note: The proposed Japanese brand name has been modified.)
[Non-proprietary name]	Eculizumab (Genetical Recombination)
[Name of applicant]	Alexion Pharma K.K.
[Date of application]	March 31, 2009
[Dosage form/Strength]	Concentrated solution for intravenous infusion: Each vial of 30 mL contains 300 mg of Eculizumab (Genetical Recombination).
[Application classification]	Prescription drug (1) Drug with a new active ingredient

[Entity]

Eculizumab is a recombinant humanized monoclonal antibody composed of the variable regions consisting of complementarity-determining regions derived from mouse anti-human complement C5α-chain monoclonal antibody and human framework regions and human IgG constant regions. The L-chain constant region is derived from a human κ-chain. The CH1, hinge and a part of CH2 regions of the H-chain constant regions are derived from human IgG2 (γ2-chain) and the rest of CH2 and CH3 regions are derived from human IgG4 (γ4-chain).
Eculizumab is produced in mouse myeloma cell (NS0).
Eculizumab is a glycoprotein (molecular weight, ca.145,235) composed of 2 H-chain molecules consisting of 448 amino acid residues each and 2 L-chain molecules consisting of 214 amino acid residues each.

Structural formulae:

H-chain

1 QVQLVQSGAE VKKPGASVKV SCKASGYIFS NYWIQWVRQA PGQGLEWMGE

51 ILPGSGSTEY TENFKDRVTM TRDTSTSTVY MELSSLRSED TAVYYCARYF

101 FGSSPNWYFD VWGQGTLVTV SSASTKGPSV FPLAPCSRST SESTAALGCL

151 VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSNFGT

201 QTYTCNVDHK PSNTKVDKTV ERKCCVECPP CPAPPVAGPS VFLFPPKPKD

251 TLMISRTPEV TCVVVDVSQE DPEVQFNWYV DGVEVHNAKT KPREEQFNST

301 YRVVSVLTVL HQDWLNGKEY KCKVSNKGLP SSIEKTISKA KGQPREPQVY

351 TLPPSQEEMT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD

401 SDGSFFLYSR LTVDKSRWQE GNVFSCSVMH EALHNHYTQK SLSLSLGK

L-chain

1 DIQMTQSPSS LSASVGDRVT ITCGASENIY GALNWYQQKP GKAPKLLIYG

51 ATNLADGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQN VLNTPLTFGQ

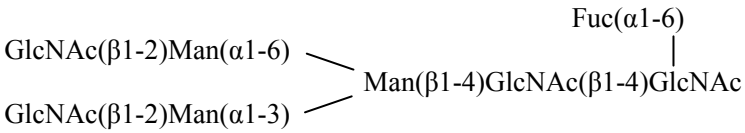
101 GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV

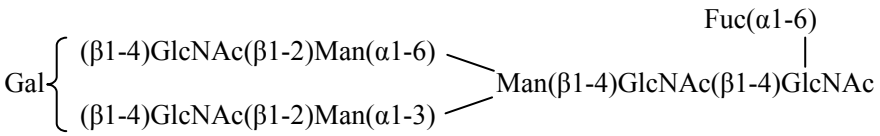
151 DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG

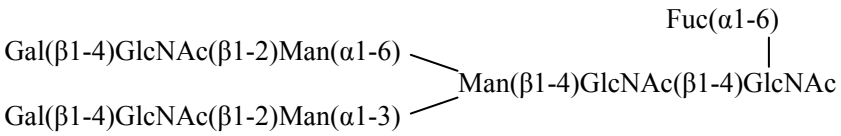
201 LSSPVTKSFN RGEC

[The amino acid sequence of Eculizumab (Genetical Recombination)]

pyroglutamic acid at Q1 of the H-chain; glycosylation at N298 of the H-chain; partial processing at K448 of the H-chain; inter-chain disulfide bonds of C136 of the H-chain−C214 of the L-chain, C224 of the H-chain−C224 of the H-chain, C225 of the H-chain−C225 of the H-chain, C228 of the H-chain−C228 of the H-chain, and C231 of the H-chain−C231 of the H-chain (intra-chain disulfide bonds are represented by solid lines); murine complementarity-determining regions (CDRs): N31 to Q35 of the H-chain, E50 to D66 of the H-chain, Y99 to V111 of the H-chain, G24 to N34 of the L-chain, G50 to D56 of the L-chain, and Q89 to T97 of the L-chain







[Predicted main carbohydrate structures of Eculizumab (Genetical Recombination)]

[Items warranting special mention]	Orphan drug (“Orphan Drug Designation” [PFSB/ELD Notification No. 1222007 dated December 22, 2008])
[Reviewing office]	Office of New Drug I

Review Results

February 18, 2010

[Brand name] Soliris for Intravenous Infusion 300mg (Note: The proposed Japanese brand name has been modified.)
[Non-proprietary name] Eculizumab (Genetical Recombination)
[Name of applicant] Alexion Pharma K.K.
[Date of application] March 31, 2009
[Results of review]
Based on the submitted data, the efficacy of the product in patients with paroxysmal nocturnal hemoglobinuria has been demonstrated. On the other hand, regarding safety, as the use of eculizumab may increase the risk of developing a meningococcal infection and a serious hemolytic crisis may occur after eculizumab discontinuation, it is necessary to inform physicians and patients of these risks and take adequate safety measures. The safety of the product is acceptable in view of its observed benefits, provided that the product is used under a proper safety control system.

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

[Indication]
Reduction of hemolysis in patients with paroxysmal nocturnal hemoglobinuria

[Dosage and administration]
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.

[Conditions for approval]
1. Due to limited data from Japanese clinical studies, conduct a post-marketing drug use-results survey over a certain period of time, covering all patients treated with Soliris, in order to obtain the background information of patients treated with Soliris, collect data on the safety and efficacy of Soliris, and take necessary measures to ensure proper use of Soliris.
2. Prior to marketing Soliris, take necessary measures to ensure that Soliris will be administered only under the supervision of a physician at a medical institution, who is familiar with the diagnosis and treatment of paroxysmal nocturnal hemoglobinuria and is also fully capable of managing the risks etc. associated with Soliris, in cooperation with a physician who is familiar with the diagnosis and treatment of meningococcal infection.

Review Report (1)

December 16, 2009

I. Product Submitted for Registration

[Brand name] Soliris for Intravenous Infusion 300 mg

[Non-proprietary name] Eculizumab (Genetical Recombination)

[Name of applicant] Alexion Pharma K.K.

[Date of application] March 31, 2009

[Dosage form/Strength] Concentrated solution for intravenous infusion: Each vial of 30 mL contains 300 mg of Eculizumab (Genetical Recombination).

[Proposed indication] Paroxysmal nocturnal hemoglobinuria (PNH)

[Proposed dosage and administration]

Soliris should be administered by intravenous infusion at a dose of 600 mg every 7 days for the first 4 weeks followed by 900 mg for the fifth dose 7 days later and then 900 mg every 14 days thereafter.

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

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

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

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired genetic disorder due to a somatic mutation of the phosphatidylinositol glycan-A (PIG-A) gene on chromosome X, which is necessary for the biosynthesis of glycosylphosphatidylinositol (GPI) anchors. The mutation leads to a deficiency of the GPI-anchored terminal complement inhibitor CD59 on the surface of clonal populations of hematopoietic stem cells. CD59 inhibits C9 binding to complement C5 and blocks the formation of the terminal complement complex C5b-9 on the red blood cell (RBC) surface. Deposition of cytolytic C5b-9 on the surface of CD59-deficient PNH RBCs results in intravascular hemolysis. PNH is characterized by recurrent episodes of hemolysis and chronic hemolysis, and intravascular hemolysis leads to hemoglobinuria and fatigue and poor physical functioning associated with anemia. It is thought that intravascular hemolysis releases excessive amount of hemoglobin (Hb), which induces the activation of platelets and blood coagulation cascade, causing thrombosis. Meanwhile, free Hb deposition in the kidney may lead to kidney diseases such as nephritis and renal tubule abnormalities.

According to the results of a 1998 survey conducted by a major research institution, the estimated

number of PNH patients in Japan is approximately 430 (Health Science Research Grants, Research Project on Intractable Diseases, Research Committee for determining the epidemiology of diseases not covered by Research Project on Treatment of Intractable Diseases, 1999 Research Results, 2000). A comparative survey between Japan and the US revealed that in Japan, the median survival time after diagnosis is 25.0 years and the main causes of death are thrombosis, haemorrhage, infections, and renal failure (*Medicine*. 2004;83:193-207.).

There are only palliative therapies for PNH that aim to relieve symptoms temporarily. Blood transfusions are used for temporarily improving the symptoms associated with anemia, short-term steroid therapy is used for acute hemolysis, and anticoagulant therapy is used to prevent and treat thrombosis. Although allogeneic hematopoietic stem cell transplantation is available as a curative option, as PNH is a slowly progressive disease, it is indicated for severe patients only, taking account of the risks associated with transplantation.

Eculizumab (Genetical Recombination) (eculizumab) is a humanized monoclonal antibody that binds with high affinity to human complement C5. Eculizumab is expected to reduce intravascular hemolysis mediated by C5b-9 by inhibiting C5 activity and the development of eculizumab for PNH patients was initiated.

Eculizumab received approval in the US in March 2007. As of October 2009, eculizumab has been approved for the indication of PNH in 33 countries including the US and Europe.

Eculizumab was designated as an orphan drug for the intended indication of "paroxysmal nocturnal hemoglobinuria" as of December 22, 2008.

2. Data relating to quality

2.A Summary of the submitted data

Eculizumab is a glycoprotein (approximately 145,235 Da) composed of two 448 amino acid heavy chains ($C_{2205}H_{3378}N_{576}O_{683}S_{19}$, approximately 49,493 Da) and two 214 amino acid light chains ($C_{1016}H_{1583}N_{271}O_{334}S_{6}$, approximately 23,130 Da) produced in a murine myeloma cell line (NS0 cell line). The molecule contains 14 disulfide bonds and there is one *N*-linked glycosylation site on the C_H2 region of the heavy chain.

Eculizumab is a humanized anti-human C5 monoclonal antibody composed of the variable regions consisting of complementarity determining regions (CDRs) derived from mouse anti-human C5α chain monoclonal antibody (m5G1.1 mAb) and human framework regions, and human IgG constant regions. The C_H1, hinge and a part of C_H2 regions of the heavy chain constant regions are derived from human IgG_2 (γ2-chain) and the rest of C_H2 and C_H3 regions are derived from human IgG_4 (γ4-chain). The light

chain constant region is derived from a human κ-chain.

2.A.(1) Drug substance

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

(a) Assembly of the expression construct and cell banking

To generate and select m5G1.1 mAb, hybridomas were generated from mice immunized with human complement component C5 and the antibodies produced by these hybridomas were evaluated for their ability to block complement-mediated hemolysis and C5a generation. The m5G1.1 mAb gene was cloned from cDNA prepared from the hybridoma. The CDRs of the genes for human heavy chain variable and C_H1 regions (hereinafter referred to as "Fd fragment") and for a human light chain were replaced by the CDRs from the genes for the variable heavy and light chains of the m5G1.1 mAb, respectively. Thus, an intermediate vector containing the gene encoding a heavy chain Fd fragment ("[redacted]") and an intermediate vector containing the gene encoding a light chain ("[redacted]") were constructed. Then, the DNA segment encoding the heavy chain formed by joining the DNA fragment encoding the heavy chain Fd fragment excised from [redacted] with a DNA fragment encoding the hinge, C_H2, and C_H3 regions, and the DNA segment encoding the light chain excised from [redacted] were inserted to construct a double-gene vector ([redacted]). The DNA segments encoding the heavy and light chains excised from the vector were inserted into a vector containing the glutamine synthetase gene, which functions as a selection marker, to generate the expression plasmid [redacted].

[redacted] was introduced by electroporation into a NS0 cell line. The cell clones selected in serum-supplemented medium containing [redacted] were adapted to serum-free medium, and pre-seed stock [redacted] of the seed cell line [redacted] was prepared. This [redacted] was cultured in the medium for preparing cell banks ([redacted]) to prepare a master cell bank (MCB) [redacted] and a working cell bank (WCB) was prepared from [redacted].

(b) Characterization and control of cell banks

The results of tests for identity and purity of the MCB, WCB, and cells at the limit of *in vitro* cell age used for production (CAL) are shown in Table 1. The results of genetic stability studies on the MCB, WCB, end of production cells (EOP), and CAL are shown in Table 2.

Table 1. Results of tests for identity and purity of cell banks and CAL

Test			Results		
			MCB	WCB	CAL
			[redacted]M	[redacted]W	[redacted] (Process [redacted])
Cell viability			Constant		NT
Isoenzyme analysis			Of mouse origin		
Mycoplasma testing (culture method, indicator cell culture method)			Negative		
Sterility test (bacteria/fungi)			No evidence of microbial growth 14 days later		NT
Tests for adventitious viruses	*In vitro* assay for adventitious viruses		Negative (Balb-C, HeLa, MRC-5, NS0, RK-13, Vero)	Negative (MRC-5, NS0, Vero)	Negative (MRC-5, NIH/3T3, Vero)
	In vitro bovine virus assay		Negative (BT, MA104)	Negative (BT, Vero)	NT
	In vivo assay to reveal latent viruses (inoculation into suckling and adult mice and guinea pigs, and in embryonated eggs)		Negative	NT	Negative
	Mouse antibody production test*		Negative	NT	Negative
	Quantitative PCR		Negative (bovine polyoma virus, bovine and porcine circovirus, MVM)	NT	Negative (MVM)
Tests for retroviruses	Transmission electron microscopy	Examination of cell sections	A-type and C-type retrovirus-like particles were observed.	NT	A-type and C-type retrovirus-like particles were observed.
		Negative staining	NT	NT	Retrovirus-like particle count < 1.4×10^5/mL
	Mink S^+L^- focus assay		Direct assay: 27 ffu/mL Extended assay: fusion foci	NT	Negative
	In vitro XC plaque assay		Negative	NT	Negative
	In vitro assay for infectious X MuLV		Negative	NT	Negative
	Reverse transcriptase activity (Mg^{2+} and Mn^{2+} dependent)		Negative	NT	Negative
	Cocultivation (MRC-5, LEX98)		Negative	NT	Negative

NT: No Tested

Balb-C: BALB/c mouse embryo cell line, BT: bovine nasal turbinate cell line, HeLa: human cervical carcinoma cell line, MA104: fetal rhesus monkey kidney cell line, MRC-5: human diploid lung cell line, MVM: minute virus of mice, NIH/3T3: mouse fibroblast cell line, RK-13: rabbit kidney cell line, Vero: African green monkey kidney cell line, X MuLV: xenotropic murine leukemia virus

*Lymphocytic Choriomeningitis Virus, Mouse Hepatitis Virus, Pneumonia Virus of Mice, Minute Virus of Mice, Sendai Virus, Ectromelia Virus, Mouse Rotavirus, Reovirus Type 3, Mouse Encephalomyelitis Virus, Mouse Adenovirus, Polyoma Virus, Hantaan Virus, Mouse Thymic Virus, Mouse Salivary Gland Virus, K Virus, Lactic Dehydrogenase Virus

Table 2. Results of genetic stability studies on cell banks, EOP, and CAL

Test item (Test method)		Results				
		MCB	WCB	EOP		CAL
		[redacted]M	[redacted]W	[redacted] (Process [redacted])	[redacted] (Process [redacted])	[redacted] (Process [redacted])
Site of integration of expression plasmid (Southern blotting)		Expected bands were detected.	Identical banding pattern with MCB			
Copy number/cell (Southern blotting)	Heavy chain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Light chain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heavy and light chain mRNA (Northern blotting)		Expected bands were detected.	NT			Identical banding pattern with MCB
cDNA sequence		Identical to the nucleic acid sequence determined for the expression construct	NT			Identical to the nucleic acid sequence determined for the expression construct

NT: No Tested

The MCB and WCB are preserved at -100°C at [redacted] sites and it has been confirmed that they are stable for [redacted] years. Whether the shelf life may be extended will be determined by assessing cell viability and cellular proliferative capacity every [redacted] years.

An additional WCB will be prepared in accordance with the current cell banking procedures based on the number of ampoules left and a newly prepared WCB will be qualified (identity [cell viability, isoenzyme analysis], purity [sterility test, mycoplasma testing, *in vitro* assay for adventitious viruses (MRC-5, NIH/3T3, Vero)]).

There is no plan for generating a new MCB.

(c) Manufacturing process

The manufacturing process and controls for the drug substance are as shown below.

Manufacturing process		Control item
Step 1	Cell thawing and inoculum preparation Cell thawing: [redacted] ampoule from WCB Medium: [redacted]	At thawing: cell [redacted]
Seed culture 1	Equipment: [redacted]mL, [redacted]mL, [redacted]mL flask ([redacted]rpm)	
Seed culture 2-5	Equipment: [redacted]mL, [redacted] mL roller bottle ([redacted]rpm)	
Seed culture 6	Equipment: [redacted]mL spinner flask ([redacted]rpm)	After Step 1 culture: [redacted] cell [redacted], cell [redacted], cell [redacted], bioburden
Step 2a	Expansion of the culture Equipment: [redacted]L bioreactor Medium: [redacted]	At Step 2a inoculation: pH, bioburden, [redacted]
Step 2b	Expansion of the culture Equipment: [redacted]L bioreactor Medium: [redacted]	During Step 2b culture: pH, bioburden, [redacted] After Step 2b culture: cell [redacted]
Step 2c	Production culture Equipment: [redacted]L bioreactor Medium: [redacted]	During Step 2c culture: pH, bioburden, [redacted] [redacted]: mycoplasma testing, test for absence of MVM[a] (quantitative PCR), *in vitro* assay for adventitious viruses (MRC-5, NIH/3T3, Vero)
Step 3	Harvest and concentration Equipment: centrifuge, depth filter ([redacted]µm), [redacted]L container, ultrafiltration membrane ([redacted]kDa)	When the volume of harvest supernatant reaches [redacted] L: bioburden After concentration: bioburden

Step 4	**Buffer exchange** **Equipment: depth filter (µm), hydrophilic membrane filter (µm)**	**After filtration: bioburden** **After storage: bioburden**
Step 5	**Affinity chromatography** **Equipment: [b] protein A column**	**At the time of loading: pH, bioburden** **After the first cycle:**
Step 6	**Virus inactivation** **Equipment: storage container** **Conditions: pH, minutes**	**During treatment: pH** **After treatment: Step , pH, bioburden, endotoxin** **Before storage: bioburden, endotoxin**
Step 7	**Concentration/buffer exchange** **Equipment: ultrafiltration membrane (kDa)**	**Before concentration: pH, electrical conductivity** **After dialysis: pH, electrical conductivity** **Before concentration adjustment: protein concentration** **After concentration adjustment: bioburden, endotoxin** **Before storage: protein concentration, pH, electrical conductivity**
Step 8	**ion exchange chromatography (non-adsorbed)** **Equipment: column** **Recovery: non-adsorbed fraction**	**At the time of loading: pH, electrical conductivity, bioburden, endotoxin** **Non-adsorbed fraction: , pH, electrical conductivity, bioburden, endotoxin**
Step 9	**Virus removal** **Equipment: (nm)** **Pressure: psig (bar)**	**After filtration: filter integrity test, bioburden, endotoxin**
Step 10	**ion exchange chromatography (bind and elute)** **Equipment: column** **Recovery: eluate fraction**	**Eluate before loading: pH, electrical conductivity, endotoxin** **At the time of loading: bioburden, endotoxin** **Eluate: bioburden, endotoxin, pooling criteria (monomer content)**
Step 11	**Preparation of drug substance (concentration/buffer exchange, addition of polysorbate 80)** **Equipment: ultrafiltration membrane (kDa)**	**Before concentration: pH, electrical conductivity** **After concentration: protein concentration** **Before permeation: pH, electrical conductivity** **After permeation: protein concentration, bioburden** **Before concentration adjustment: protein concentration** **After addition of polysorbate 80: protein concentration**
Step 12a	**Final sterile filtration and filling** **Equipment: L LDPE[c] bag with hydrophilic membrane filter (µm)**	**After filtration: filter integrity test, bioburden**
Step 12b	**Storage** **Condition: 2°C-8°C**	

: Steps – , –

a) MVM (minute virus of mice)

b)

c) Very low density polyethylene

Process validation of the commercial-scale manufacturing process for the drug substance was carried out and analyses have been performed for the following parameters in addition to the above control items.

Cell growth profile (cell number, viability, population doubling rate, , , etc.) and product yield and its quality attributes (SDS-PAGE [CBB staining], isoelectric focusing [IEF]) for the fermentation process and the processing time and the percent yield and yield of product for the harvesting step have been determined.

For the purification process, the percent yield of product at each step and monomer content at each chromatographic step and virus removal step have been determined and reducing/non-reducing

SDS-PAGE and IEF have been carried out at each chromatographic step. Removal of process-related impurities and product-related impurities has been evaluated and host cell protein (HCP), host cell DNA, bovine serum albumin (BSA), antifoaming agents [redacted] and [redacted], and cholesterol are reduced by affinity chromatography, aggregates (dimers), HCP, host cell DNA, BSA, and protein A are reduced by [redacted] ion exchange chromatography (non-adsorbed), and aggregates are reduced by [redacted] ion exchange chromatography (bind and elute) and it has been confirmed that impurities can be controlled at a certain level or lower. Furthermore, re-filtration using a virus removal membrane or a membrane filter for the final sterile filtration has been evaluated at scales of 1/[redacted] or 1/[redacted], respectively, and re-filtration can be carried out up to [redacted] times each, respectively, for each drug substance lot and if re-filtration is actually carried out, its impact on product quality and the integrity of the membrane filter are to be determined. The re-use of each column has also been evaluated and it has been confirmed that at a commercial scale, [redacted] ([redacted]) protein A[redacted] column, [redacted] column (non-adsorbed), and [redacted] column (bind and elute) maintain consistent purification performance for up to [redacted], [redacted], and [redacted] re-uses, respectively. The re-use of an ultrafiltration membrane has also been evaluated and it was confirmed that the membrane can be used consistently for up to [redacted] re-uses at a scale of 1/[redacted] of Step 7, which was selected as the worst case scenario, and up to [redacted] re-uses of ultrafiltration membranes for Steps 7 and 11 are allowed. The storage conditions for intermediates obtained at different steps have been established based on the results of stability studies and sterility test, as shown in Table 3.

Table 3. Storage conditions for intermediates obtained at different steps

Intermediate	Container	Maximum allowable holding time	
		[redacted]°C	[redacted]°C
Filtrate after the end of Step 4	**Stainless container**	**[redacted] days**	**[redacted] hours[a)]**
Treated solution after the end of Step 6 **Filtrate after the end of Step 7**	**LDPE bag (after sterile filtration)**	**[redacted] days**	**[redacted] days**
Non-adsorbed fraction from column after the end of Step 8	**Stainless container**	**[redacted] hours**	**[redacted] hours**
	LDPE bag (after sterile filtration)	**[redacted] days**	**[redacted] days**
Filtrate after the end of Step 9	**Stainless container**	**[redacted] hours**	**[redacted] hours**
	LDPE bag (after sterile filtration)	**[redacted] days**	**[redacted] days**
Loading solution for column in Step 10	**Stainless container**	**-**	**[redacted] hours**
Column eluate after the end of Step 10	**Stainless container** **LDPE bag (after sterile filtration)**	**[redacted] hours**	**[redacted] hours**
Drug substance solution after the end of Step 11	**Stainless container**	**[redacted] hours**	**[redacted] hours**

[a)] Storage temperature is 25°C.

(d) Adventitious agents safety evaluation

i) Non-viral adventitious agents

The raw materials of animal origin used in the drug substance manufacturing process are New Zealand-sourced fetal bovine serum as a medium component in the preparation of the MCB and the preservation of the current WCB and US-sourced BSA and ovine cholesterol sourced from Australia or New Zealand as media components for cell banking and cell culture. These raw materials are derived from healthy animals and the absence of infectious contaminants has been confirmed by the supplier and manufacturer. Moreover, BSA that does not conform to the Standards for Biological Ingredients has been confirmed to meet a threshold to provide safety assurance in accordance with “Handling of Risk

Assessment etc. in Partial Change Applications for Drugs, Medical Devices, etc., Using Bovine Derived Raw Materials etc." (PFSB/ELD Notification No. 0801001 dated August 1, 2003). A partial change application for switching to BSA sourced from another country will be filed by the 4th quarter of 2011.

ii) Adventitious viruses etc.

Tests of purity were performed on the MCB, WCB, and CAL, and the absence of contamination by mycoplasma, bacteria, infectious retroviruses, and adventitious viruses have been confirmed. Mycoplasma testing, test for the absence of MVM, and *in vitro* assay for adventitious viruses are performed at the unprocessed bulk level in the fermentation process, endotoxin and bioburden are assessed at each purification step, and furthermore, sterility test is performed at the formulation step. Therefore, the manufacturing process of the drug substance is controlled against adventitious agents. The capacity of each purification step to clear viruses is shown in Table 4.

Table 4. Results of viral clearance studies

Purification process	Virus reduction factor (Log_{10})				
	X MuLV	HSV	BAV	POL	MVM
Affinity chromatography	[redacted] a), b)	[redacted] b), c)	[redacted] c), d)	[redacted] c)	[redacted]
Virus inactivation (pH[redacted], [redacted] minutes)	[redacted] c)	[redacted] c)	[redacted]	[redacted]	[redacted]
[redacted]ion exchange chromatography (non-adsorbed)	[redacted] c), d)	[redacted] c), d)	[redacted]	[redacted]	[redacted]
Virus removal (pore size [redacted] nm)	[redacted] c)	[redacted]4 c)	[redacted] c)	[redacted]	[redacted] c)
Overall reduction factor	**≥ 16.98** c)	**≥ 16.33** e)	**≥ 7.66** e)	**3.91**	**4.59**

NR: No Reduction, NT: No Tested
BAV (bovine adeno virus), HSV (herpes simplex virus), MVM (minute virus of mice),
POL (poliovirus), X MuLV (xenotropic murine leukemia virus)

a) Quantitative PCR
b) As inactivation of eluted viruses by elution buffer (pH[redacted]) has not been confirmed, the reduction factor is not included in an overall reduction factor.
c) 50% tissue culture infectious dose: $TCID_{50}$
d) Virus reduction factor for used resin
e) The sum of the individual factors

(e) Manufacturing process development (Comparability)

The drug substance manufacturing process has undergone four changes during product development (Processes A-D; Process E is the commercial process). Of the main clinical studies in PNH patients, a foreign phase III clinical study (C04-001 [TRIUMPH]), a foreign phase III clinical study (C04-002 [SHEPHERD]), and their extension study (E05-001) used clinical trial material produced by Process D or E and a Japanese clinical study (C07-001) and its extension study (E07-001) used clinical trial material produced by Process E.

The seed cell line for the preparation of the MCB was changed from [redacted] to [redacted] that was of the same origin and had higher expression, which was used in Processes B to E. The fermentation process was scaled up from [redacted] L at the early stage of development to [redacted] L or [redacted] L in Process B, [redacted] L in Processes C and D, and [redacted] L in Process E. In the purification process, protein A derived from *Staphylococcus aureus* to be used in the affinity chromatographic step was changed to [redacted] protein A (genetical recombination) produced without using raw materials of biological origin and pH[redacted] treatment time in the virus inactivation step was changed from [redacted] to [redacted] minutes to [redacted] to [redacted] minutes,

which were employed in Processes C to E. In order to consistently reduce an increase in aggregates as observed in 1 drug substance lot produced by Process C, [redacted] ion exchange chromatographic step was included in Process D. That step was further changed to [redacted] ion exchange chromatographic step in Process E in order to optimize the process. The pore size of a membrane filter for the virus removal step was changed from [redacted] nm to [redacted] nm, which was employed in Process E.

The comparability of the drug substances before and after manufacturing process changes has been demonstrated by comparing the results of specification tests and characterization studies between post-change drug substance and pre-change reference material.

2.A.(1).2) Structure/Composition

The following characterization studies were performed.

(a) Primary structure

i) Amino acid composition

After hydrolysis, each amino acid was quantified. As a result, the determined amino acid composition agreed with the theoretical values deduced from the cDNA sequence.

ii) N-terminal and C-terminal amino acid sequences

・No heterogeneity of the heavy- and light-chain N-terminal amino acid sequences was detected by Edman degradation. The heavy chain N-terminus was modified with pyroglutamic acid.

・Although no heterogeneity of the light-chain C-terminal amino acid residues was detected by nano-electrospray ionization-tandem mass spectrometry, the C-terminal Gly^{487} or Lys^{488} residue of the heavy chain was detected at a level of [redacted]% or [redacted]%, respectively.

iii) Peptide map

・The protein was reduced, alkylated and digested with trypsin and the obtained peptides were analyzed using reverse-phase chromatography-electrospray ionization-mass spectrometry (RP HPLC-ESI-MS). The results were consistent with the amino acid sequence deduced from cDNA.

・A glycosylation site was identified at Asn298 of the heavy chain CH2 region. No aglycosylation of tryptic peptide T21 (amino acid residues 294-302 of the heavy chain) was detected.

・The deamidation rate was about [redacted]% for T22 (amino acid residues 303-318 of the heavy chain) and [redacted]% for T32 (amino acid residues 372-393 of the heavy chain).

iv) Carbohydrate structure

・Monosaccharide compositional analysis was performed and four monosaccharides (fucose, mannose, galactose [Gal], and *N*-acetylglucosamine [GlcNAc]; about [redacted], [redacted], [redacted], and [redacted] nmol/mg, respectively) were identified and *N*-acetylgalactosamine was not detected, which indicated that eculizumab has no *O*-linked glycosylation. Sialic acid analysis was performed. As a result, the content of

N-glycolylneuraminic acid (Neu5Gc) was about [redacted] mmol/mol and *N*-acetylneuraminic acid was detected in trace amount, but was below the lower limit of quantification (≤ [redacted] mmol/mol). Carbohydrate constitutes about [redacted]% of the mass of eculizumab.

・Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS) or anion exchange chromatography of fluorescently labeled *N*-linked glycans was performed. As a result, fucosylated biantennary *N*-linked glycans with zero, one, or two non-reducing terminal Gal residue(s) (G0F, G1F, G2F; [redacted]%-[redacted]% in total) were mainly detected and glycans lacking the terminal GlcNAc (G0F-GN) and high mannose-type glycans (Man5) were slightly detected. Furthermore, αGal (Galα1-3Gal) glycans were detected at levels of [redacted]% to [redacted]% (size profile of glycans). Neutral and sialylated oligosaccharides were detected at levels of [redacted]% to [redacted]% and [redacted]% to [redacted]%, respectively (glycan charge profile).

(b) Physicochemical properties

i) Molecular weight

MALDI-TOF-MS and ESI-TOF-MS indicated that the molecular weight of the molecule is in agreement with the theoretical molecular mass of 147,870 Da.

ii) Electrophoretic patterns

・IEF showed [redacted] major bands and [redacted] to [redacted] minor bands within a pI range of [redacted] to [redacted].

・SDS-PAGE (CBB staining) yielded two major bands (heavy and light chains) and [redacted] minor bands whose intensities were below the lower limit of quantification (staining intensity, [redacted]%) (antibodies lacking [redacted] light chain, antibodies lacking [redacted] light chain and [redacted] heavy chain [[redacted] form]) under reducing conditions and one major band (monomer, ≥ [redacted]%), [redacted] minor bands (antibodies lacking [redacted] light chain, antibodies lacking [redacted] light chains, ≤ [redacted]% and ≤ [redacted]%, respectively), and [redacted] bands whose intensities were below the lower limit of quantification ([redacted] form, [redacted] different light chain fragments) under non-reducing conditions.

iii) Liquid chromatographic patterns

・Size exclusion chromatography (GE HPLC) yielded a main peak (monomer, ≥ [redacted]%) and a minor high molecular weight peak presumed to represent aggregates (≤ [redacted]%). The molecular weights of monomer and aggregates as determined by LC-ESI-TOF-MS matched the theoretical molecular masses of eculizumab and the dimer, respectively. The potency of aggregates (C5 binding assay) was about [redacted]%. Aggregates produced percent hemolysis of [redacted]% at [redacted] μg/mL and [redacted]% at [redacted] μg/mL, which were lower than monomer ([redacted]% and [redacted]%, respectively).

・Weak acid cation exchange column chromatography yielded one main peak and broad peaks unresolved from the main peak ([redacted] acidic peaks and [redacted] basic peaks).

・Reverse-phase chromatography yielded a single main peak and when the protein was reduced and alkylated, [redacted] main peaks (heavy and light chains) and [redacted] minor peaks were observed.

・Hydrophobic interaction chromatography yielded a single main peak.

iv) Higher order structure

・The concentration of free sulfhydryl groups in eculizumab as determined by Ellman's assay was below the lower limit of quantification (10 μM).

・Analysis of non-reduced, alkylated tryptic peptides by RP HPLC-ESI-MS confirmed that 28 (14 pairs) out of a total of 36 Cys residues form disulfide bonds within the heavy chain, within the light chain, and between the heavy and light chains (Cys^{22} of the heavy chain-Cys^{96} of the heavy chain, Cys^{136} of the heavy chain-Cys^{214} of the light chain, Cys^{149} of the heavy chain-Cys^{205} of the heavy chain, Cys^{262} of the heavy chain-Cys^{322} of the heavy chain, Cys^{368} of the heavy chain-Cys^{426} of the heavy chain, Cys^{23} of the light chain-Cys^{88} of the light chain, Cys^{134} of the light chain-Cys^{194} of the light chain).

・Near-ultraviolet and far-ultraviolet circular dichroism (CD) yielded the spectra that are characteristic of an antibody. The wavelength of maximum absorption was [redacted] nm and the wavelength of minimum absorption was [redacted] nm. The percentage of β-sheet structure was about [redacted]%.

(c) Biological properties

・The binding affinity of eculizumab for human C5 (dissociation constant), association rate constant, and dissociation rate constant, as determined by surface plasmon resonance, were approximately [redacted] pM, approximately [redacted]$\times 10^{5}$ $M^{-1}s^{-1}$, and approximately [redacted]$\times 10^{-5}$ s^{-1}, respectively, at [redacted]°C and were approximately [redacted] pM, approximately [redacted]$\times 10^{6}$ $M^{-1}s^{-1}$, and approximately [redacted]$\times 10^{-4}$ s^{-1}, respectively, at [redacted]°C.

・The functional complement inhibition activity of eculizumab in human serum was assessed using a hemolytic assay measuring the hemoglobin release from chicken red blood cells. Eculizumab produced percent hemolysis of > [redacted]% at [redacted] μg/mL, but < [redacted]% at [redacted] μg/mL, and almost completely inhibited hemolysis at [redacted] μg/mL.

・Since eculizumab has an IgG_2-IgG_4 heavy chain backbone, eculizumab is not considered to exhibit complement-dependent cytotoxicity activity or antibody-dependent cell-mediated cytotoxicity (ADCC) activity.

・[redacted] mAb epitope mapping ([redacted] and [redacted] using [redacted] or [redacted], and [redacted] various domains [redacted] and its [redacted]) indicated that [redacted]-terminal [redacted] domain of the human C5α chain is recognized as an epitope.

2.A.(1).3) Product-related substances

Heavy chain N-terminal pyroglutamate, loss of C-terminal lysine residue of the heavy chain, deamidation, oligosaccharide variants, and charge variants have been detected.

2.A.(1).4) Impurities

(a) Process-related impurities

It has been confirmed that the media components used in the cell culture process, i.e. [redacted], [redacted], and cholesterol are removed to below the lower limit of quantification ([redacted] ppm, [redacted] µg/mL, and [redacted] ng/mL, respectively) by the affinity chromatographic step. Protein A, BSA, HCP, and host cell DNA are reduced in the purification process (< [redacted] ng/mg, < [redacted] ng/mg, < [redacted] ng/mg, and < [redacted] pg/mg, respectively) and listed as impurities in the drug substance specification.

(b) Product-related impurities

Antibody fragments have consistently been detected as minor bands on reducing/non-reducing SDS-PAGE (CBB staining) [see "2.A.(1).2) Structure/Composition (b) Physicochemical properties ii) Electrophoretic patterns"]. The impurities that increase during the shelf-life of the drug substance or the drug product are aggregates identified on reducing/non-reducing SDS-PAGE (CBB staining) and GE HPLC and acidic variants identified by IEF.

2.A.(1).5) Drug substance specification

The proposed specifications for the drug substance are description (appearance), identification (peptide map, size profile of glycans, IEF), osmolality, pH, purity (protein A, BSA, HCP, host cell DNA), polysorbate 80, test for total viable count, bacterial endotoxins, reducing/non-reducing SDS-PAGE (CBB staining), GE HPLC, hemolytic assay, C5 binding assay, and protein concentration.

2.A.(1).6) Stability of drug substance

Using commercial scale lots of the drug substance stored in [redacted] mL LDPE bags, long-term testing (2°C-8°C, 24 months, 3 lots) and accelerated testing ([redacted]°C-[redacted]°C, [redacted] months, 3 lots; [redacted]°C-[redacted]°C, [redacted] months, 1 lot) were conducted and the following stability information was evaluated: description (appearance), peptide map, IEF, osmolarity, pH, reducing/non-reducing SDS-PAGE (CBB staining), GE HPLC, sterility test, bacterial endotoxins, hemolytic assay, C5 binding assay, and protein concentration. At the long-term storage condition, although an increase of aggregates associated with a [redacted]% to [redacted]% decrease of monomers were detected by GE HPLC, there were no marked changes in other attributes tested up to 24 months. At the accelerated condition, the percentage of acidic bands on IEF increased from [redacted]% to [redacted]% at the initial timepoint to [redacted]% to [redacted]%, an increase of aggregates associated with a [redacted]% to [redacted]% decrease of monomers were detected by GE HPLC, and reducing SDS-PAGE (CBB staining) showed about [redacted]% decreases in the heavy and light chains. Since the formulation of the drug product is the same as that of the drug substance, stress testing was performed on the drug product.

Based on the above, a shelf life of 18 months has been proposed for the drug substance when stored in [redacted] L LDPE bags at 2°C to 8°C, protected from light.

2.A.(2) Drug product

2.A.(2).1) Formulation development

The drug product is an injectable solution and each glass vial contains 300 mg of Eculizumab (Genetical Recombination), the active ingredient, in 30 mL of product solution and the other ingredients are 263.1 mg sodium chloride as an isotonizing agent, 13.8 mg sodium dihydrogenphosphate monohydrate and 53.4 mg disodium hydrogenphosphate heptahydrate as buffering agents, 6.6 mg polysorbate 80 as a stabilizer, and the appropriate amount of water for injection as a solvent. The vial contains an overfill of 1.7 mL.

2.A.(2).2) Drug product manufacturing process

The formulated drug substance is mixed (mixing process), sterile filtered using a hydrophilic membrane filter ([redacted] μm), filled into colorless glass vials, stoppered with siliconized butyl rubber stoppers, and sealed with aluminum seals with polypropylene flip-off caps (sterile filtration/filling/closing process) and packaged (packaging process) and primarily stored at 2°C to 8°C (storage process). The vials are allowed to adjust to room temperature, labelled, and secondary packaged and then stored at 2°C to 8°C (packaging/storage process). The sterile filtration/filling/closing, storage, and packaging/storage processes have been defined as critical process steps. As in-process control tests, test for total viable count during the mixing process, filter integrity test and sterility test during the sterile filtration process, fill weight testing during the filling process, visual inspection during the packaging process, and visual inspection during the packaging/storage process are performed. IEF and hemolytic assay are performed at release. [redacted] to [redacted] at [redacted] ([redacted]) or [redacted] ([redacted]) and [redacted].

During the drug product development, the volume was changed from [redacted] mL to [redacted] mL and [redacted] mL, and then to 30 mL, but the formulation did not change.

2.A.(2).3) Drug product specification

The proposed specifications for the drug product are description (appearance), identification (peptide map), osmolarity, pH, reducing/non-reducing SDS-PAGE (CBB staining), GE HPLC, bacterial endotoxins, sterility test, extractable volume, insoluble particulate matter, foreign insoluble matter, C5 binding assay, and protein concentration.

2.A.(2).4) Stability of drug product

Stability studies of the drug product are summarized in Table 5.

Table 5. Summary of stability studies of drug product

Stability testing	Test attributes	Test results	
		[redacted]	[redacted]
Long-term testing 2°C-8°C 36 months Protected from light Upright and inverted positions	description (appearance), pH, osmolarity, peptide map, IEF, reducing/non-reducing SDS-PAGE (CBB staining), GE HPLC, sterility test, bacterial endotoxins, insoluble particulate matter, C5 binding assay, protein concentration	3 lots The percentage of acidic bands on IEF increased from [redacted]% at the initial time point to [redacted]% and an increase of aggregates associated with a [redacted]% decrease of monomers were detected by GE HPLC, but there were no marked changes in other attributes tested up to 36 months.	3 lots Stable up to 3 months. Testing will continue up to 36 months.
Accelerated testing 1 20°C-25°C 12 months Protected from light Inverted position	description (appearance), pH, osmolarity, peptide map, IEF, reducing/non-reducing SDS-PAGE (CBB staining), GE HPLC, C5 binding assay, bacterial endotoxins, protein concentration	3 lots As the percentage of the major band on IEF decreased from [redacted]% at the initial time point to [redacted]%, a new band was detected. An increase of aggregates associated with a [redacted]% decrease of monomers were detected by GE HPLC. A new band with a slight increase of aggregates were detected by non-reducing SDS-PAGE. Increases of low and high molecular weight bands with about [redacted]% decreases of heavy and light chains were detected by reducing SDS-PAGE.	—
Accelerated testing 2 23°C-27°C 12 months Protected from light Inverted position	description (appearance), pH, osmolarity, IEF, reducing/non-reducing SDS-PAGE (CBB staining), GE HPLC, hemolytic assay,[1] C5 binding assay, bacterial endotoxins, protein concentration	1 lot Stable up to [redacted] months. Testing will continue up to [redacted] months.	3 lots A slightly broader range of pIs was detected by IEF at [redacted] months, but there were no changes in other attributes tested. Testing will continue up to [redacted] months.
Stress testing[2] (a) Forced degradation low pH, high pH, oxidation, deamidation, storage at high temperature (b) Extreme temperature • High temperature ([redacted] hours): [redacted]°C-[redacted]°C, [redacted]°C-[redacted]°C • Low temperature ([redacted] days): [redacted]°C-[redacted]°C (c) [redacted] temperature cycles [redacted]°C-[redacted]°C ([redacted] days) followed by [redacted]°C-[redacted]°C ([redacted] days) [redacted]°C-[redacted]°C ([redacted] days) followed by [redacted]°C-[redacted]°C ([redacted] days) • [redacted]°C-[redacted]°C ([redacted] days) followed by [redacted]°C-[redacted]°C ([redacted] hours) (d) Photostability Light exposure condition ([redacted] million lx·h, [redacted] W·h/m²) Ambient temperature (e) Vibration 2°C-8°C	(a)-(e): description (appearance), reducing/non-reducing SDS-PAGE (CBB staining), IEF, GE HPLC (d) (light-protected samples only): pH, osmolarity, insoluble particulate matter (a) and (d) (light-protected samples only) peptide map, hemolytic assay (a), (c)-(e): C5 binding assay (c)-(e): protein concentration	(a) pH[redacted]: Degradation occurred. pH[redacted]: Stable for [redacted] days. Oxidation: Degradation occurred. Deamidation: Degradation occurred. 40°C: Stable for [redacted] hours. (b) Comparable to controls. (c) Comparable to controls. (d) Following light exposure, a decrease of monomers was detected by GE HPLC, a decrease of monomers was detected by non-reducing SDS-PAGE, and a decrease of the major band and a new minor band were detected by IEF. Comparable to controls when protected from light. (e) Comparable to controls.	—

1) Not performed for DSM.
2) Upright position for (b) and inverted position for others.

In addition to the above studies, a preliminary study to explore the storage conditions for reference materials was conducted. As a result, a decrease of monomers was detected by GE HPLC when stored frozen ([redacted]°C, [redacted]°C) vs. refrigerated (2°C-8°C). Therefore, taking account of the impact of prolonged freezing on drug product quality, a shelf-life of 30 months has been proposed for the drug product when stored at 2°C to 8°C, protected from light.

The drug product was diluted with each intravenous solution (Isotonic Sodium Chloride Solution, JP;

Glucose Injection, JP [5%]; or Ringer's Solution, JP) to the final concentration of 5 mg/mL. The stability of the diluted solutions when stored at 2°C to 8°C or 20°C to 25°C for up to 72 hours was assessed. As a result, there were no marked changes in description (appearance), IEF, reducing/non-reducing SDS-PAGE (CBB staining), GE HPLC, hemolytic assay, or C5 binding assay in each solution.

2.A.(3) Reference materials

The current reference materials, [redacted] and [redacted] are drug substances produced in accordance with the drug substance manufacturing process (Process E) (Lot numbers, [redacted] and [redacted]) and stored at 2°C to 8°C. Reference materials should meet the drug substance specification and should be tested for quality attributes (IEF, reducing/non-reducing SDS-PAGE [CBB staining], GE HPLC, hemolytic assay, C5 binding assay, protein concentration) and characterized (monosaccharide compositional analysis, sialic acid analysis, glycan charge profile, molecular weight [MALDI-TOF-MS, ESI-MS], N-terminal amino acid sequencing, CD).

The tentative shelf-life of the reference materials is [redacted] years and the stability of the reference materials during storage will be assessed by evaluating the quality attributes every [redacted] years and whether the shelf life may be extended will be determined.

A new reference material will be prepared in accordance with the current drug substance manufacturing process based on the shelf-life and the amount left and a newly prepared reference material will be tested for quality attributes and characterized.

2.B Outline of the review by PMDA

2.B.(1) Evaluation of disulfide bond heterogeneity

Though eculizumab has an IgG_2-IgG_4 heavy chain backbone and different patterns of disulfide bonds between Cys residues are expected compared with other IgG subclasses, inter-heavy chain disulfide bonds involving 8 residues in the hinge regions of the two heavy chains (Cys^{224}-Cys^{224}, Cys^{225}-Cys^{225}, Cys^{228}-Cys^{228}, Cys^{231}-Cys^{231}) have not been detected. Thus, PMDA asked the applicant if the patterns of disulfide bonds in eculizumab have been fully analyzed and if their consistency is controlled.

The applicant conducted an additional study, identified peptides containing 9 different hinge regions by ESI-Q-TOF-MS, and presented the structures of 3 different disulfide bond variants deduced from the detected peptides. The applicant responded that although these variants are considered to be consistently present, it is technically difficult to control the variants quantitatively.

Although it is understood that quantitative control is difficult, PMDA is asking the applicant to show their view on the need to control the heterogeneity of these variants, taking account of the possible

effects of these variants on the safety and efficacy of eculizumab.

2.B.(2) Control of immunogenic glycans

Since eculizumab contains fucosylated biantennary *N*-linked oligosaccharides bearing immunogenic Neu5Gc or αGal (including Galα1-3Gal), PMDA asked the applicant to explain the influences of glycan structure and its heterogeneity on the safety of eculizumab. In terms of ensuring safety, PMDA is also asking the applicant to explain the need to include the Neu5Gc content in the specification and provide a justification for the specification limit for the αGal content.

2.B.(3) C5 binding assay

PMDA asked the applicant to explain the reasons for changing the C5 binding assay method and for variability in assay values despite the principle of the assay being the precise ELISA (enzyme-linked immunosorbent assay) method and provide a justification for the specification limits.

The applicant responded as follows:

Although biotinylated protein L was used for the detection of eculizumab bound to C5 protein in the old assay, as the production of the detection reagents including this reagent and the detector was discontinued, a new assay has been employed, which uses HRP (horseradish peroxidase)-labeled mouse anti-human IgG_4 antibody for detection. Although the values obtained with the new assay are about [redacted]% lower than those obtained with the old assay, the robustness of the new assay has been demonstrated through a validation study. The values obtained with the new assay for the internal standard, the clinical formulation, and the proposed commercial formulation were within a range of 800,000 to 1,200,000 BU/mg, as with the old assay. The change to the new assay was approved by EMEA in April 2009 and FDA in June 2009.

PMDA is asking the applicant to provide a justification for the specification limits, taking account of the values obtained with the new assay for the clinical formulation and the proposed commercial formulation that have been used in patients.

2.B.(4) Drug product specification

2.B.(4).1) Inclusion of foreign insoluble matter test

PMDA asked the applicant to consider including Foreign Insoluble Matter Test for Injections, JP in the drug product specification.

The applicant responded that although foreign insoluble matters have never been detected so far, Foreign Insoluble Matter Test will be included in the specification.

PMDA accepted the response.

2.A.(4).2) Inclusion of IEF and hemolytic assay

PMDA is asking the applicant to explain the reason for not including IEF and hemolytic assay in the specification in Japan despite IEF and hemolytic assay being included in the drug product specification in the US and Europe and the basis for considering that the quality of the drug product can be assured by the results of these tests performed at the time of its release.

3. Non-clinical data

3.(i) Summary of pharmacology studies

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

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

There are three pathways of complement activation and C3a and C3b are formed from C3 in all three pathways. C3b cleaves C5 into C5a and C5b. C5a has anaphylatoxin activity and leukocyte chemotactic activity and induces mast cell degranulation, vascular hyperpermeability, and smooth muscle contraction etc. C5b interacts with C6 to C9, allowing for the formation of the complex C5b-9 and C5b-9 causes cell lysis. As eculizumab is an anti-C5 antibody, the potency of each anti-C5 antibody was assessed by measuring hemolytic activity* and C5a generation.

3.(i).A.(1).1) Generation of eculizumab (4.2.1.1.1-4.2.1.1.3, Studies GTR49, GTR56, and GTR52)

Murine anti-human C5 (hC5) mAbs were screened and m5G1.1 mAb as an inhibitor of both hemolytic activity (complete inhibition at [redacted] μg/mL) and C5a generation (complete inhibition at [redacted] μg/mL) was selected. The K_D of m5G1.1 mAb for hC5 was 29.5 pmol/L.

In order to reduce immunogenicity in humans, the CDRs of m5G1.1 mAb were inserted into a human antibody (h5G1.1) and using the Fab region of the generated antibody (h5G1.1 Fab (CDR)), the capacity to compete with m5G1.1 mAb for binding to hC5 was compared. As a result, the Fab region of m5G1.1 mAb and h5G1.1 Fab (CDR) exhibited similar capacities to compete with m5G1.1 mAb for binding to hC5 at [redacted] ng/mL to [redacted] μg/mL. Thus, the applicant explained that humanization of the framework regions had no effect on the hC5 binding capacity of the antibody.

For further humanization, an antibody containing the variable regions of h5G1.1 Fab (CDR), human κ light-chain constant regions, and hybrid human IgG_2-IgG_4 heavy-chain constant regions, which have been reported to be unable to activate complement or bind to the Fc-γ receptor of effector cells (h5G1.1 G2/G4 mAb: eculizumab), was generated.

* Chicken erythrocytes sensitized with anti-chicken erythrocyte antibody were added to human serum for hemolysis.

3.(i).A.(1).2) C5 inhibition activity of eculizumab (4.2.1.1.4 and 4.2.1.1.6, Studies GTR84 and BP 26FR)

Eculizumab, h5G1.1 G4 mAb[†], and m5G1.1 mAb inhibited human serum-mediated hemolysis of chicken erythrocytes sensitized with anti-chicken erythrocyte antibody (almost complete inhibition at 100 μg/mL, [redacted] μg/mL, and [redacted] μg/mL, respectively) and the applicant explained that the difference in the heavy-chain constant regions were shown not to affect C5 inhibition activity.

In another study, eculizumab almost completely blocked human serum-mediated hemolysis of chicken erythrocytes sensitized with anti-chicken erythrocyte antibody at 25 μg/mL, but did not inhibit hemolysis in rhesus monkey, baboon, chimpanzee, cynomolgus monkey, pig, rabbit, rat, or guinea pig sera even at 100 μg/mL.

3.(i).A.(1).3) Affinity of eculizumab for hC5 (4.2.1.1.5, Study GTR109)

The K_D of eculizumab for hC5 (mean ± standard deviation [SD]) was 46 ± 1.6 pmol/L (25°C) or 120 ± 5.5 pmol/L (37°C).

3.(i).A.(1).4) Epitope mapping of hC5 (4.2.1.1.7, Study GTR55)

Epitope mapping of hC5 using m5G1.1 mAb was performed, which indicated that the antibody recognizes the amino acid sequences at positions 822 to 826 (DVFLE), 879 to 883 (KSSKC), and 930 to 933 (VPEG) as an epitope cluster.

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

3.(i).A.(2).1) Cross-reactivity with human tissues (4.2.1.2.1, Study PAI-IM1184)

The potential cross-reactivity of eculizumab (5 and 30 μg/mL) with cryosections of normal human tissues was evaluated by immunostaining. As a result, eculizumab staining was observed in smooth and striated muscle in various tissues, myoepithelium, myofibroblasts, renal tubular epithelium, reticulum cells, and platelets etc. The applicant discussed that eculizumab is not considered to have cross-reacted with human tissues because (a) C5 expression in vascular smooth muscle cells and heart muscle have been demonstrated (*Microbiol Immunol.* 1999;43:585-593, *Circ Res.* 1998;83:860-869.), (b) C5 is a secreted protein and is not expressed on cell surface (*Annu Rev Immunol.* 1995;13:277-305.), and (c) the staining likely represents staining of intracellular C5 as acetone fixation and cryotomy of the tissue/cell samples expose intracellular sites.

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

Since eculizumab has high selectivity for hC5 and is species-specific, no safety pharmacology studies have been conducted.

[†] An antibody containing the variable regions of h5G1.1 Fab (CDR), human κ light-chain constant regions and human IgG4 heavy-chain constant regions

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

3.(i).B.(1) Efficacy of eculizumab in PNH

PNH arises from the deficiency of the GPI-anchored terminal complement inhibitor CD59 on hematopoietic stem cells. Since CD59 inhibits C9 binding to complement C5 and blocks the formation of the terminal complement complex C5b-9 on the RBC surface, the deficiency of CD59 on PNH RBCs leads to deposition of cytolytic C5b-9 on the surface, which results in hemolysis.

Eculizumab binds to hC5, preventing the formation of C5b-9 by inhibiting the cleavage of C5 and is expected to reduce C5b-9-mediated hemolysis.

Although non-clinical pharmacology studies submitted in the application have not demonstrated hemolytic inhibitory activity *in vivo*, as there is no animal model of PNH and eculizumab was created as an antibody against hC5 and did not inhibit hemolysis in non-human sera, suggesting that eculizumab does not inhibit C5 in sera of other species, the lack of a non-clinical *in vivo* study to demonstrate efficacy of eculizumab was unavoidable. On the other hand, since *in vitro* studies using eculizumab showed that eculizumab binds to hC5 and inhibits human serum-mediated hemolysis, it can be inferred that eculizumab reduces hemolysis by inhibiting the cleavage of C5 and preventing the formation of C5b-9.

However, many of *in vitro* studies were performed once. Data from repeated studies were needed for explanation in order to check the reproducibility of studies.

3.(i).B.(2) Cross-reactivity of eculizumab

PMDA's view on the applicant's discussion that eculizumab does not cross-react with various human tissues is as follows:

It has been reported that C5 is a secreted protein and is not expressed on cell surface and it has also been explained that secreted proteins were fully removed. Thus, an inference that the observed staining was due to the binding of eculizumab to intracellular C5 is understandable. However, since the cross-reactivity study of eculizumab with human tissues was conducted by the methods that expose intracellular sites, it is difficult to determine whether eculizumab staining of tissues represents eculizumab binding to cell surface or intracellular sites of tissues. If eculizumab cross-reacts with the cell surface of tissues, there should be potentially some effects on biological functions. However, except for headache, there were no particular adverse events reported at a higher incidence by the eculizumab group than by the placebo group in a clinical study (C04-001 [TRIUMPH]). The applicant discussed the mechanism of eculizumab-induced headache as follows: hemolysis inhibition by eculizumab leads to reduced free Hb, which scavenges nitric oxide (NO), and increased free NO dilates blood vessels, causing headache. However, as the mechanism is undefined, the possible involvement of the cross-reactivity of eculizumab can not be excluded.

PMDA asked the applicant about findings on the cross-reactivity of eculizumab with complements other than C5 or cytokines. The applicant responded that no cross-reactivity study of eculizumab with complements other than C5 or cytokines had been conducted.

PMDA considers as follows:
If eculizumab cross-reacts with complements other than C5 or cytokines, the immune function will be affected. However, as no marked increase in the incidence of infection-related adverse events was observed in the clinical study (C04-001 [TRIUMPH]), the possibility that the cross-reactivity of eculizumab with complements other than C5 or cytokines leads to clinically immediately relevant events has not been suggested so far.

3.(i).B.(3) Safety pharmacology
Since no safety pharmacology studies of eculizumab have been performed, PMDA asked the applicant to explain the effects of eculizumab on the central nervous, cardiovascular, and respiratory systems based on the results from toxicity and clinical studies, etc.

The applicant explained as follows:
In a 26-week intravenous injection toxicity study in mice of a murine anti-C5 antibody, BB5.1 mAb, there were no effects on the central nervous, cardiovascular, or respiratory systems at the doses inhibiting hemolytic activity [see "3.(iii).A.(2) Repeat-dose toxicity"]. In clinical studies, except for headache, there were few adverse events involving central nervous, cardiovascular, or respiratory system, etc. Therefore, it is considered that eculizumab has no significant effects on the central nervous, cardiovascular, or respiratory systems.

PMDA considers as follows:
Since eculizumab was developed as an antibody against hC5 and there is no cross-reactivity of eculizumab with C5 from other species and eculizumab is a humanized antibody except for the CDRs, it is understood that safety pharmacology evaluation is difficult. On the other hand, there were no treatment-related effects on the central nervous, cardiovascular, or respiratory systems at the doses inhibiting hemolytic activity in the 26-week repeat-dose toxicity study in mice of a murine anti-C5 antibody, BB5.1 mAb. Thus, non-clinical data indicate that there are no effects of C5 inhibition on the central nervous, cardiovascular, and respiratory systems.

See "4.(iii).B.(5) Safety" for the safety of eculizumab in clinical studies.

3.(ii) Summary of pharmacokinetic studies

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

Since eculizumab binds specifically to hC5, a C5-deficient mouse model reconstituted with hC5, and an IgG_4 isotype of eculizumab (h5G1.1 G4 mAb), which is identical in amino acid sequence to eculizumab except that it contains the human IgG_4 heavy-chain constant region, instead of eculizumab, were used to determine the serum concentrations of the antibody over time and assess hemolytic activity.‡

The hC5 and h5G1.1 G4 mAb levels were determined by ELISA assay.

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

3.(ii).A.(1).1) Single-dose studies (4.2.2.2.1, Studies GTR-0104.00 and GTR-0104.01)

Male mice were intravenously or subcutaneously injected a single dose of h5G1.1 G4 mAb at 5, 17, 50, 100, or 150 µg, or 190 µg of 2A2 HuG4§ as a negative control antibody, or vehicle (0.2 mL phosphate-buffered saline) and hemolytic activity inhibition was assessed for up to 48 hours after injection. Hemolytic activity inhibition was detected from 2 minutes until 48 hours following the intravenous administration of 50 to 150 µg of h5G1.1 G4 mAb and hemolytic activity inhibition was detected, but delayed by 24 hours following the subcutaneous injection of 50 µg.

Female mice were intravenously or subcutaneously injected a single dose of 50 µg of h5G1.1 G4 mAb or 60 µg of 2A2 HuG4 and serum h5G1.1 G4 mAb and 2A2 HuG4 concentrations over time were determined. Serum h5G1.1 G4 mAb concentrations over time following the single intravenous or subcutaneous administration of 50 µg of h5G1.1 G4 mAb are shown in Figure 1.

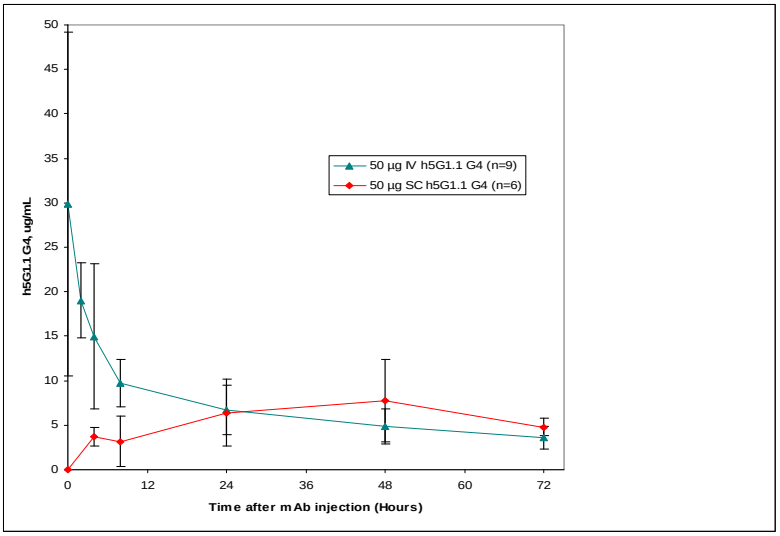


Figure 1. Serum h5G1.1 G4 mAb concentrations over time following single administration of h5G1.1 G4 mAb

‡ Chicken erythrocytes sensitized with anti-chicken erythrocyte antibody were added to mouse serum for hemolysis.

§ An unrelated antibody with a human IgG_4 heavy-chain constant region

3.(ii).A.(2) Distribution, metabolism, excretion, and pharmacokinetic drug interactions

As eculizumab and h5G1.1 G4 mAb bind to a soluble protein, hC5, which is secreted into the blood and do not bind to murine C5, a distribution (organ/tissue distribution, protein binding, placental transfer, etc.), metabolism, excretion, or pharmacokinetic drug interaction study has not been performed.

The applicant discussed as follows:

Generally, placental transfer of maternal IgG antibodies to the fetus is known and antibodies are excreted in milk. Thus, eculizumab is also expected to cross the placenta and be excreted in milk.

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

3.(ii).B.(1) Non-clinical pharmacokinetic studies

PMDA considers as follows:

Since eculizumab, developed as an antibody against hC5, does not demonstrate cross-reactivity with C5 from other species and is a humanized antibody except for the CDRs, the lack of non-clinical pharmacokinetic assessment of eculizumab was unavoidable. The h5G1.1 G4 mAb concentrations over time determined in mice are just reference information because a C5-deficient mouse model reconstituted with hC5 was used and the heavy-chain constant region structure of h5G1.1 G4 mAb, which was used instead of eculizumab, is different from that of eculizumab, and it is difficult to predict the pharmacokinetics of eculizumab in humans.

3.(iii) Summary of toxicology studies

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

Since eculizumab binds specifically to hC5 and did not inhibit hemolysis in sera from the non-human animals studied [see "3.(i).A.(1).2) C5 inhibition activity of eculizumab"], a non-clinical toxicity study of eculizumab has not been performed. However, using a surrogate murine anti-murine C5 monoclonal antibody, BB5.1 mAb, 26-week repeat-dose and reproductive and developmental toxicity studies in mice were conducted to evaluate the long-term treatment effects of C5 inhibition on tissue toxicity and reproductive function. BB5.1 mAb is a full-length monoclonal antibody of IgG_1 isotype and its amino acid sequence is different from that of eculizumab, but publications (*J Clin Invest*. 2005;115:1590-1600, etc.) have reported that BB5.1 mAb binds specifically to murine C5 and blocks C5b-9 activity and C5a activity *in vitro* and *in vivo*.

For serum BB5.1 mAb concentrations, percent hemolysis at each timepoint was measured using a serum complement hemolytic activity assay system [see "3.(i).A.(1).2) C5 inhibition activity of eculizumab"] and a lower percent hemolysis compared with the control group was a qualitative indicator of systemic exposure.

3.(iii).A.(1) Single-dose toxicity

No single-dose studies have been conducted.

3.(iii).A.(2) Repeat-dose toxicity (4.2.3.2-1 and 4.2.3.2-2, Studies 6709-108 and 6709-109)

Female mice were intravenously administered vehicle (20 mM Tris-buffered saline three times weekly) or 30 mg/kg of BB5.1 mAb once, twice, or three times weekly (30, 60, or 90 mg/kg/week) for 4 weeks. No toxic signs were observed. The percent hemolysis was 92% to 94% in the control group, 3% to 34% in the once weekly (30 mg/kg/week) group, 1% to 13% in the twice weekly (60 mg/kg/week) group, and 0% to 15% in the three times weekly (90 mg/kg/week) group. Since hemolytic activity was similar for mice treated with BB5.1 mAb twice weekly (60 mg/kg/week) and three times weekly (90 mg/kg/week), it was concluded that the highest dose of BB5.1 mAb in future toxicology studies is 60 mg/kg/week.

Female or male mice were intravenously administered vehicle (20 mM Tris-buffered saline twice weekly) or 30 mg/kg of BB5.1 mAb once or twice weekly (30 or 60 mg/kg/week) for 26 weeks (a 4-week recovery period was scheduled for mice in the control and 60 mg/kg/week groups). Five mice (3 males and 2 females) in the 60 mg/kg/week group died and the cause of deaths was unknown. Even in the control group, 4 deaths (3 males and 1 female) occurred. As there were no toxicologically significant changes, the no observed adverse effect level (NOAEL) was determined to be 60 mg/kg/week.

The mean percent hemolysis was 68.3% to 86.6% in the control group (including prior to initiation of treatment and after a 4-week recovery), 13.3% to 18.8% in the 30 mg/kg/week group (during treatment), and 3.9% to 21.0% in the 60 mg/kg/week group (during treatment). The mean percent hemolysis was 41.7% in females and 67.5% in males (after a 4-week recovery) and there was no particular gender-related difference.

3.(iii).A.(3) Genotoxicity and carcinogenicity

Eculizumab is specific to hC5 and does not have cell proliferative activity or growth factor-like activity and it was considered that genotoxic substances are unlikely to arise from the manufacturing process of eculizumab. Thus, no genotoxicity or carcinogenicity studies have been conducted.

3.(iii).A.(4) Reproductive and developmental toxicity

Although the placental transfer of eculizumab or BB5.1 mAb has not been studied, as BB5.1 mAb is an IgG_1 antibody, it is inferred that it may cross the placenta.

3.(iii).A.(4).1) Study of fertility and early embryonic development to implantation (4.2.3.5.1.1, Study 6709-104)

Mice were intravenously administered vehicle (20 mM Tris-buffered saline twice weekly) or 30 mg/kg of BB5.1 mAb once or twice weekly (30 or 60 mg/kg/week). Male mice were dosed from 4 weeks prior to mating until 1 or 2 days prior to necropsy and female mice were dosed from 2 weeks prior to mating, throughout the mating period, and until gestation day 7. Although dose-related, reduced body weight gain, reduced food consumption, and decreased prostate gland weight were observed in males, there were no abnormalities in copulation index, sperm motility, or epididymal sperm count, etc. There were no abnormalities in clinical signs or reproductive performance in females. The NOAELs for parental general toxicity, parental reproductive toxicity, and embryo-fetal viability were all determined to be 60 mg/kg/week.

The percent hemolysis (mean ± SD) was 90.2 ± 11.9% (at Week 4) and 100.0 ± 0.0% (at Week 10) in males and 98.4 ± 3.0% (on gestation day 12) in females in the control group, 24.6 ± 16.5% (at Week 4) and 27.2 ± 14.6% (at Week 10) in males and 50.6 ± 46.0% (on gestation day 12) in females in the 30 mg/kg/week group, and 7.0 ± 6.2% (at Week 4) and 16.2 ± 10.1% (at Week 10) in males and 50.6 ± 29.5% (on gestation day 12) in females in the 60 mg/kg/week group.

3.(iii).A.(4).2) Embryofetal development study (4.2.3.5.2.1, Study 6709-105)

Pregnant mice were intravenously administered vehicle (20 mM Tris-buffered saline twice weekly) or 30 mg/kg of BB5.1 mAb once or twice weekly (30 or 60 mg/kg/week) from gestation day 6 to gestation day 15. There were no abnormal findings in dams. In fetuses, one case of malrotated hindlimbs and one case of cleft palate were observed at 30 mg/kg/week, but not at 60 mg/kg/week and therefore, these findings were considered unrelated to BB5.1 mAb. At 60 mg/kg/week, one case of umbilical hernia and two cases (from two different litters) of unilateral retinal dysplasia (folded retina: a severe fold or multiple folds of the retina) were observed and these findings were considered related to BB5.1 mAb.

Evaluations for the umbilical hernia and folded retinas observed in mouse fetuses were performed by an external consultant. According to a report by Research Triangle Institute international, a laboratory and research organization (RTI project No. 08412.007), these findings did not occur. There is a case in which fetal retinal folds were shown to be artifacts produced by the process of tissue preparation (*Toxicol Appl Pharmacol.* 1976;35:347-354.) and although congenital retinal dysplasia should be usually bilateral, the retinal dysplasia was unilateral in this study and there were no other intraocular abnormalities or haemorrhage, etc. Therefore, the applicant explained that the folded retinas may have been artifacts. The development of umbilical hernia was assessed as unknown relationship to BB5.1 mAb.

The NOAEL was determined to be 60 mg/kg/week for maternal general and reproductive toxicity and

the NOAEL for fetal developmental toxicity was determined to be 30 mg/kg/week as umbilical hernia was noted at 60 mg/kg/week.

The percent hemolysis (mean ± SD) (on gestation day 18) was 78.0 ± 43.8% in the control group, 52.6 ± 49.0% in the 30 mg/kg/week group, and 62.4 ± 37.8% in the 60 mg/kg/week group.

3.(iii).A.(4).3) Study for effects on pre- and postnatal development, including maternal function (4.2.3.5.3.1, Study 6709-107)

Pregnant mice were intravenously administered vehicle (20 mM Tris-buffered saline twice weekly) or 30 mg/kg of BB5.1 mAb once or twice weekly (30 or 60 mg/kg/week) from gestation day 6 to lactation day 18. There were no abnormal findings in maternal animals or pups and the NOAELs for maternal general toxicity and reproductive performance and for F_1 pups were both determined to be 60 mg/kg/week.

The percent hemolysis (mean ± SD) (on lactation day 14) was 95.6 ± 7.0% in the control group, 80.6 ± 20.5% in the 30 mg/kg/week group, and 83.6 ± 16.6% in the 60 mg/kg/week group.

Pregnant and lactating mice in the above 1) to 3) reproductive and developmental toxicity studies exhibited higher percent hemolysis (50.6%-80.6% at 30 mg/kg/week and 50.6%-83.6% at 60 mg/kg/week [mean]) than the non-pregnant female mice in the 26-week repeat-dose toxicity study (13.3%-14.5% at 30 mg/kg/week and 3.9%-4.6% at 60 mg/kg/week). The applicant inferred that pregnancy and lactation may have affected the amount of complement or the complement inhibitory function of the antibody, but the cause is unknown.

3.(iii).A.(5) Local tolerance

No local tolerance studies have been performed with eculizumab or other anti-C5 antibodies. However, BB5.1 mAb or vehicle-related local irritation at the injection site was not observed in repeat-dose or reproductive and developmental toxicity studies.

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

3.(iii).B.(1) Retinal dysplasia

PMDA's view on the retinal dysplasia observed in an embryofetal development study is as follows:

The conducting laboratory concluded that the folded retinas were due to a teratogenic effect of BB5.1 mAb, whereas the applicant explained that the folded retinas were not related to BB5.1 mAb, based on the inference mainly from the background data for the cases of folded retina and the case of artifacts. However, histopathological findings of the retinas, hemolytic inhibition in the dams of normal fetuses vs. the dams of the fetuses with folded retinas, or receptor distribution in ocular tissue, etc. have not been examined based on the data from this study. Therefore, the applicant's explanation that the folded

retinas were not related to BB5.1 mAb is not based on solid evidence and like umbilical hernia, whether the folded retinas were related to BB5.1 mAb or not is unknown.

Umbilical hernia and folded retinas were observed in the high dose group (60 mg/kg/week) only and the incidence of umbilical hernia was 0.4% (1 of 230 offspring) and the incidence of folded retina was 1.7% (2 of 114 offspring). In addition, the two cases of folded retina were unilateral and there were no abnormalities in clinical observations or necropsy findings of offspring born to mothers exposed to BB5.1 mAb (388 offspring) in a study for effects on pre- and postnatal development, including maternal function (6709-107). Furthermore, no effects on the eyes of the offspring of women who were treated with eculizumab during pregnancy have been reported in clinical studies or foreign post-marketing surveillance [see "4.(iii).B.(8).2) Use during pregnancy or lactation"]. Taking account of the above, although it is necessary to provide information on these findings, there is little need for further investigation.

3.(iii).B.(2) Toxicity studies using an anti-C5 antibody other than eculizumab

PMDA's view on the use of an anti-C5 antibody other than eculizumab in toxicity studies submitted in the application is as follows:

Although the amino acid sequence of either the variable or constant region of BB5.1 mAb, an anti-C5 antibody used in place of eculizumab, is not similar to that of eculizumab, it has been reported that BB5.1 mAb binds specifically to murine C5 and inhibits hemolytic activity in mice (*J Clin Invest*. 2005; 115:1590-1600, etc.). Toxicity studies with BB5.1 mAb evaluated chronic effects and reproductive and developmental effects at doses that demonstrated the reduction of the mean percent hemolysis by C5 inhibition, which showed no toxicity findings. Therefore, C5 inhibition is unlikely to result in chronic toxicity or reproductive and developmental toxicity. As no toxicity studies with eculizumab have been conducted, the effects of eculizumab other than those of C5 inhibition are unknown.

However, since eculizumab does not cross-react with C5 from other species, toxicological evaluation based on studies with eculizumab is difficult. Therefore, toxicological evaluation is inevitably based on studies with BB5.1 mAb.

4. Clinical data

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

The to-be-marketed formulation was used in all clinical studies submitted as evaluation data in the application.

Concentrations of eculizumab, soluble C5b-9 (sC5b-9) and human anti-human antibodies (HAHA) in human serum were measured using an ELISA method and an electro-chemiluminescent immunoassay.

No data from biopharmaceutic studies have been submitted.

4.(ii) Summary of clinical pharmacology studies

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

4.(ii).A.(1) Studies using human biomaterials

No data from studies using human biomaterials have been submitted.

4.(ii).A.(2) Japanese phase II clinical study (5.3.4.2.6 and 5.3.5.2.6, Study C07-001 [20 to 20])

See "4.(iii).A.(1) Japanese phase II clinical study (C07-001)" for a brief description of the study.

Pharmacokinetic analysis showed that the trough serum concentrations of eculizumab (mean ± standard error [SE]) at Week 2 and Week 12 were 90.5 ± 6.25 μg/mL and 116.5 ± 10.93 μg/mL, respectively. The pharmacokinetic parameters estimated by a population pharmacokinetic (PPK) analysis with a 1-compartmental model are shown in Table 6.

Table 6. Estimated pharmacokinetic parameters using a 1-compartmental model

CL (L/h)	V_d (L)	K_{el} (1/h)	$t_{1/2}$ (h)
0.0173 ± 0.00633	6.09 ± 1.417	0.00288 ± 0.000928	265.6 ± 83.9

Mean ± SD, n = 26

Pharmacodynamic analysis showed that the proportion of patients with hemolytic activity values ≤ 20%[**] was 62.1% (18 of 29 patients) at Week 1 and reached 93.1% (27 of 29 patients) at Week 8 and at Week 12. The pharmacodynamic parameters for hemolytic activity estimated using the cumulative Weibull function are shown in Table 7.

Table 7. Estimated pharmacodynamic parameters using the cumulative Weibull function

E_0 (%)	E_{diff} (%)	C_{deff} (μg/mL)	sf
100.2 ± 34.54	96.7 ± 33.34	36.5 ± 18.05	2.61

Mean ± SD, n = 27

E_0: hemolytic activity at baseline, E_{diff}: theoretical maximal inhibitory effect,

C_{deff}: eculizumab concentration required to produce 1/e (36.8%) effect, sf: slope of PK/PD relationship

[**] At least 100 serum samples from healthy adults were assayed for hemolytic activity and a cutoff value of 20% ("mean minus 3SD") was chosen based on the idea that hemolytic activity of ≤ 20% represents complete blockade of terminal complement activity in serum.

4.(ii).A.(3) Foreign phase I clinical study (5.3.5.2.1, Study C02-001 [May 2002 to January 2003]; *N Engl J Med.* 2004;350:552-558.)

See "4.(iii).A.(3) Foreign phase I clinical study (C02-001)" for a brief description of the study.

Pharmacokinetic analysis showed that the trough serum concentrations of eculizumab (mean ± SD) at Week 10 and Week 12 were 108.1 ± 55.33 μg/mL and 70.2 ± 20.13 μg/mL, respectively, and the peak serum concentrations of eculizumab at Week 4 and Week 10 were 259.12 ± 51.47 μg/mL and 201.09 ± 96.28 μg/mL, respectively, and the applicant explained that serum concentrations did not reach a steady-state by Week 12.

Pharmacodynamic analysis showed that ≤ 20% hemolytic activity was maintained from Week 3 to Week 12 in 90.9% of patients (10 of 11 patients).

4.(ii).A.(4) Foreign phase I clinical study (5.3.5.2.2, Study E02-001 [August 2002 to December 2003]; *Blood*. 2005;106:2559-2565.)

See "4.(iii).A.(4) Foreign phase I clinical study (E02-001)" for a brief description of the study.

Pharmacokinetic analysis showed that the trough serum concentrations of eculizumab (mean ± SD) at baseline (after 12 weeks of treatment), Week 28 (after 40 weeks of treatment), and Week 52 (after 64 weeks of treatment) were 81.8 ± 48.54 μg/mL, 166.9 ± 102.1 μg/mL, and 112.4 ± 46.88 μg/mL, respectively.

Pharmacodynamic analysis showed that the level of hemolytic activity was ≤ 20% at all timepoints in all patients up to Week 52.

4.(ii).A.(5) Foreign phase II clinical studies (5.3.5.2.3, Studies X03-001 and X03-001A [August 2003 to December 2005]; *Haematologica*. 2005;90:ECR40.)

See "4.(iii).A.(5) Foreign phase II clinical studies (X03-001 and X03-001A)" for a brief description of the studies.

Pharmacokinetic analysis showed that the trough serum concentrations of eculizumab (mean ± SD) at baseline (after 64 weeks of treatment) and Week 50 (after 114 weeks of treatment) were 106.8 ± 47.62 μg/mL and 80.5 ± 37.26 μg/mL, respectively.

Pharmacodynamic analysis showed that although the level of hemolytic activity exceeded 20% in one patient each at Weeks 4, 42, and 50, the level of hemolytic activity was ≤ 20% at all timepoints in the remaining patients.

4.(ii).A.(6) Foreign phase III clinical study (5.3.5.1.1, Study C04-001 [TRIUMPH] [August 2004 to December 2005]; *Br J Haematol.* 2008;142:263-272, *N Engl J Med.* 2006;355:1233-1243.)

See "4.(iii).A.(6) Foreign phase III clinical study (C04-001)" for a brief description of the study.

Pharmacokinetic analysis showed that the trough serum concentrations of eculizumab (mean ± SE) in the eculizumab and placebo groups were 113.5 ± 8.70 μg/mL and 10.1 ± 0.08 μg/mL, respectively, at Week 4 and 101.8 ± 10.8 μg/mL and 10.1 ± 0.09 μg/mL, respectively, at Week 26.

Pharmacodynamic analysis showed that the proportions of patients with hemolytic activity values ≤ 20% at Week 4 and Week 26 were 100.0% (42 of 42 patients) and 97.6% (41 of 42 patients), respectively.

4.(ii).A.(7) Foreign phase III clinical study (5.3.4.2.5 and 5.3.5.2.4, Study C04-002 [SHEPHERD] [December 2004 to October 2006]; *Blood.* 2008;111: 1840-1847, *Br J Haematol.* 2008;142:263-272.)

See "4.(iii).A.(7) Foreign phase III clinical study (C04-002)" for a brief description of the study.

Pharmacokinetic analysis showed that the trough serum concentrations of eculizumab (mean ± SE) at Week 4 and Week 52 were 104.5 ± 5.08 μg/mL and 110.3 ± 8.92 μg/mL, respectively. The pharmacokinetic parameters estimated by a PPK analysis with a 1-compartmental model are shown in Table 8.

Table 8. Estimated pharmacokinetic parameters using a 1-compartmental model

CL (mL/h/kg)	V_d (mL/kg)	K_{el} (1/h)	$t_{1/2}$ (h)
0.3349 ± 0.13401	113.93 ± 28.719	0.003077 ± 0.0013682	261.07 ± 90.795

Mean ± SD, n = 97

Pharmacodynamic analysis showed that the proportions of patients with hemolytic activity values ≤ 20% at Week 4 and Week 52 were 95.8% (91 of 95 patients) and 84.9% (79 of 93 patients), respectively. The pharmacodynamic parameters for hemolytic activity estimated using an E_{max} model with Hill coefficient are shown in Table 9. The applicant discussed that the very large Hill coefficient indicated that eculizumab inhibits C5 at low concentrations.

Table 9. Estimated pharmacodynamic parameters using an E_{max} model with Hill coefficient

E_0 (%)	E_{max} (%)	EC_{50} (μg/mL)	Hill coefficient
90.14 ± 4.418	88.14 ± 4.583	31.509 ± 7.8152	7.2521 ± 2.82334

Mean ± SD, n = 97

E_0: hemolytic activity at baseline, E_{max}: theoretical maximal inhibitory effect

EC_{50}: eculizumab concentration required to produce 50% of E_{max}

4.(ii).A.(8) Foreign phase III clinical study (5.3.4.2.4 and 5.3.5.2.5, Study E05-001 [May 2005 to March 2006 (Interim report)])

See "4.(iii).A.(8) Foreign phase III clinical study (E05-001)" for a brief description of the study.

The pharmacokinetic parameters estimated by a PPK analysis with a 1-compartmental model are shown

in Table 10.

Table 10. Estimated pharmacokinetic parameters using a 1-compartmental model

CL (mL/h/kg)	V_d (mL/kg)	K_{el} (1/h)	$t_{1/2}$ (h)
0.329 (39.0%)	113.0 (23.7%)	0.0030 (41.4%)	263 (34.2%)

Mean (CV%), n = 141

The pharmacodynamic parameters for hemolytic activity estimated using the cumulative Weibull function are shown in Table 11.

Table 11. Estimated pharmacodynamic parameters using the cumulative Weibull function

E_0 (%)	E_{diff} (%)	C_{deff} (μg/mL)	sf
93.8 (9.35%)	91.0 (9.56%)	30.6 (27.2%)	2.61 (43.5%)

Mean (CV%), n = 141

E_0: hemolytic activity at baseline, E_{diff}: theoretical maximal inhibitory effect

C_{deff}: eculizumab concentration required to produce 1/e (36.8%) effect, sf: slope of PK/PD relationship

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

4.(ii).B.(1) Relationship between serum eculizumab concentration and hemolytic activity

The applicant explained that eculizumab is effective at serum concentrations of ≥ 35 μg/mL and described its rationale as follows:

Eculizumab concentrations below 35 μg/mL tended to result in an increased level of hemolytic activity in a clinical study in patients with idiopathic membranous glomerulopathy (C99-004) and it was shown that ≥ 35 μg/mL of eculizumab blocked C5 (as assessed by measuring hemolytic activity) in ≥ 90% of blood samples obtained from all clinical studies conducted before Study C99-004 (Investigator's Brochure, Eculizumab. Version 11, 28 July 2005 [Alexion Pharmaceuticals Inc. In-house material]).

On the other hand, the serum concentrations of C5 in 7 normal volunteers were 99 to 134 μg/mL and the serum concentrations of C5 in 21 patients with diseases associated with C3 or C5 abnormalities were 86 to 122 μg/mL (*J Clin Invest*. 1977;59:704-715.). Eculizumab binds to C5, blocks its cleavage into C5a and C5b, and inhibits terminal complement activity. Theoretically, one molecule of eculizumab binds to two molecules of C5. Taking account of these findings, as 35 μg/mL of eculizumab (about 236 nM; molecular weight, about 148 kDa) is considered to bind to 95 μg/mL of C5 (about 500 nM; molecular weight, about 196 kDa) in human serum, a serum eculizumab concentration of "35 μg/mL" has been chosen as a threshold for efficacy.

The relationship between serum concentration and hemolytic activity in clinical studies in PNH patients (C02-001, TRIUMPH, SHEPHERD, C07-001) also showed that serum trough concentrations of ≥ 35 μg/mL are sufficient to maintain a hemolytic activity of ≤ 20% in the majority of patients (see Figure 2).

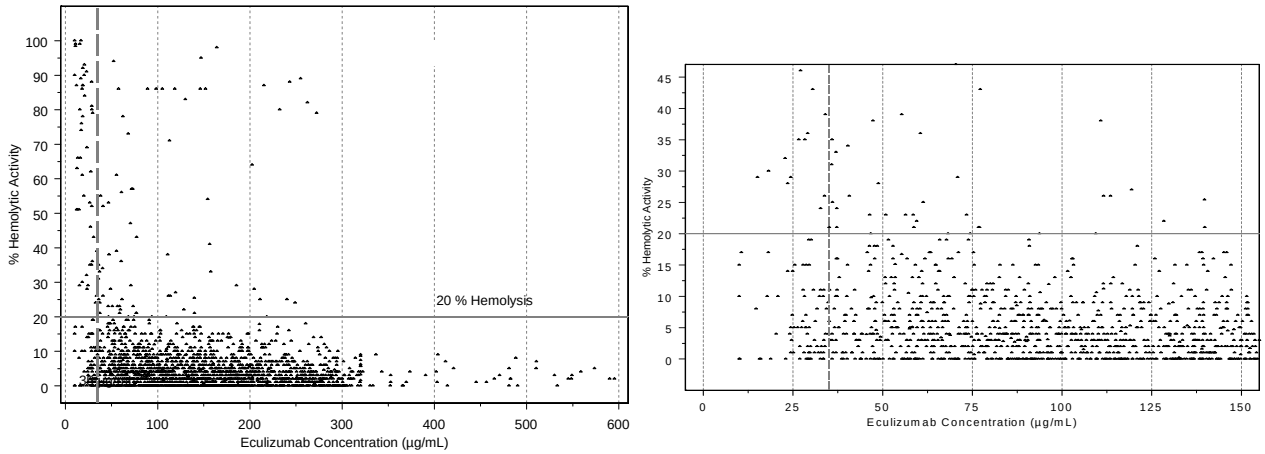


Figure 2. Relationship between serum eculizumab concentration and hemolytic activity in PNH patients (Left figure, All plots; Right figure, Magnification of the plots)

PMDA considers as follows:

With respect to the relationship between eculizumab serum concentration and hemolytic activity, as shown in Figure 2, the level of hemolytic activity was < 20% at serum concentrations of ≥ 35 μg/mL in the majority of samples (89.8% [1886 of 2101 samples]) while the level of hemolytic activity was ≥ 20% even at serum concentrations of ≥ 35 μg/mL in some patients (4.1% [87 of 2101 samples]). Therefore, serum concentrations of eculizumab ≥ "35 μg/mL" do not necessarily sufficiently inhibit hemolysis in all patients. However, taking account of the results from the TRIUMPH study, the efficacy of eculizumab can be expected at the proposed dosage regimen [see "4.(iii).B.(4) Efficacy" and "4.(iii).B.(7) Dosage and administration"].

4.(ii).B.(2) Pharmacokinetics/pharmacodynamics in Japan and overseas

The applicant explained about differences in the pharmacokinetics and pharmacodynamics (hemolytic activity) of eculizumab between Japan and overseas as follows:

Although the CL and Vc estimated from a PPK analysis in Japanese PNH patients are as shown in Table 6, when adjusted for body weight (mean ± SD), the CL was 0.282 ± 0.0870 mL/h/kg and the Vc was 101.9 ± 27.51 mL/kg, which were similar to the CL and Vc estimated from a PPK analysis in foreign PNH patients (see Table 8 and Table 10).

Observed serum concentrations of eculizumab over time in a Japanese clinical study (C07-001) and foreign clinical studies (C02-001, TRIUMPH, SHEPHERD) are as shown in Figure 3 and there were no particularly major differences.

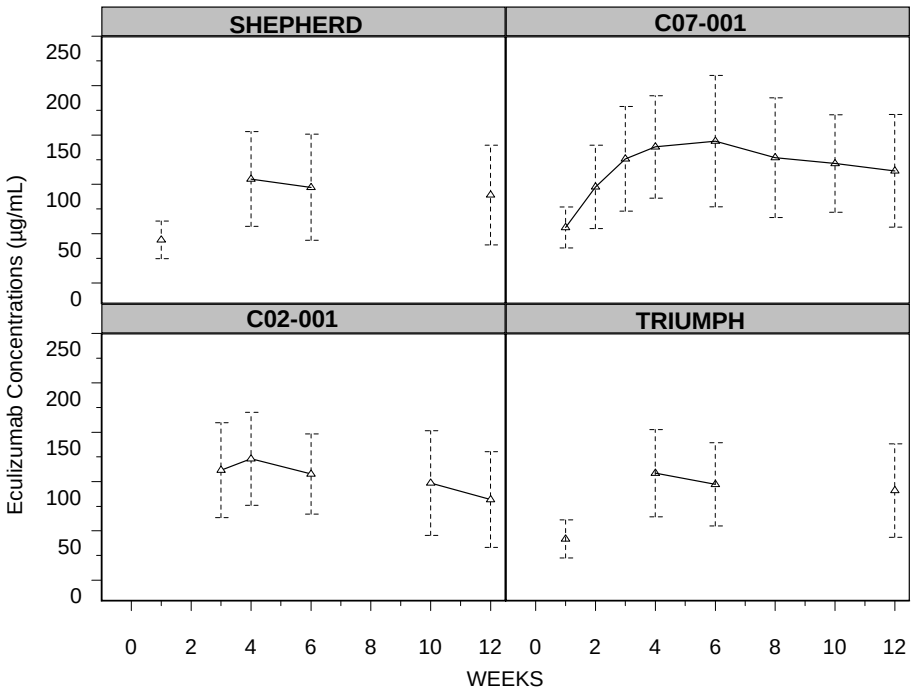


Figure 3. **Serum eculizumab concentrations over time in clinical studies (C02-001, TRIUMPH, SHEPHERD, C07-001)**

Furthermore, as to the pharmacodynamics of eculizumab, though figures showing the measured hemolytic activity over time in the Japanese clinical study (C07-001) and foreign clinical studies (TRIUMPH, SHEPHERD) are currently being prepared, the eculizumab pharmacodynamic parameters for hemolytic activity estimated using the cumulative Weibull function were similar between Japan and overseas (see Table 7 and Table 11).

The data from all Japanese and foreign studies in PNH patients (C02-001, TRIUMPH, SHEPHERD, E05-001, C07-001; a total of 177 patients) were pooled and the PK/PD relationship of eculizumab was investigated. As a result, although the statistically significant covariates were an effect of body weight on CL and Vc and an effect of gender on CL, there were no particular differences in the pharmacodynamic effect (hemolytic activity) except for Week 1. The CL of eculizumab (C02-001, TRIUMPH, SHEPHERD, and C07-001 were pooled; mean ± SD) was 0.0268 ± 0.0115 L/h in male patients and 0.0182 ± 0.0071 L/h in female patients and there were no major differences.

Based on the above, although the pharmacokinetics of eculizumab in Japanese and foreign PNH patients may be slightly different due to the effect of body weight, the pharmacodynamic effect is similar and there are no particular differences in the safety profile of eculizumab between Japan and overseas. Therefore, no dose adjustment should be required for Japanese PNH patients.

PMDA considers as follows:
Concerning the pharmacokinetics and pharmacodynamics of eculizumab in Japan and overseas, the observed pharmacokinetic data were compared, PPK analysis was performed and the pharmacodynamic parameters were estimated using the cumulative Weibull function. As a result, since blood trough concentrations over time were slightly higher in Japanese PNH patients with lower body weight compared with foreign PNH patients, body weight may affect eculizumab blood concentrations over time. However, though the results of the pharmacodynamic hemolytic assay from Japanese and foreign clinical studies are currently being requested, there were no particular differences in the pharmacodynamic parameters (hemolytic activity) estimated using the cumulative Weibull function between Japan and overseas and there was also little difference in the CL value estimated from a PPK analysis between Japan and overseas. Therefore, differences in the pharmacokinetics of eculizumab due to the effect of body weight are unlikely to significantly affect inhibition of hemolysis by eculizumab.

The above analysis indicated the possibility that body weight affects the pharmacokinetics of eculizumab and safety data from Japanese and foreign clinical studies (TRIUMPH, SHEPHERD, C07-001) showed higher incidences of nasopharyngitis, headache, and eczema, etc. in Japanese PNH patients than in foreign PNH patients [see "4.(iii).B.(5) Safety"]. As Japanese patients tend to have lower body weight than foreign patients, PMDA is currently asking the applicant about the effects of body weight on the safety and efficacy of eculizumab.

4.(ii).B.(3) HAHA induction and its impact on the pharmacokinetics of eculizumab
Based on the results from Japanese and foreign clinical studies of eculizumab, the applicant explained the impact of HAHA induction on the pharmacokinetics of eculizumab as follows:
A total of 940 patients including non-PNH patients were treated with eculizumab in Japanese and foreign clinical studies. There was no apparent impact of HAHA induction on the pharmacokinetic parameters of eculizumab.

Among PNH clinical studies, there were no patients with a positive HAHA response in Studies C02-001, E02-001, and X03-001. Although 1 patient in the placebo group and 1 patient in the eculizumab group had a positive HAHA response in the TRIUMPH study and 2 patients had a positive HAHA response in the SHEPHARD study, there was no apparent impact on the pharmacokinetics of eculizumab. In Study C07-001, there were 3 patients with positive HAHA response before eculizumab treatment, but none after eculizumab treatment. No analysis has been performed for Study E05-001.

PMDA considers as follows:

An assay method to detect HAHA used in studies other than the Japanese clinical study (C07-001) was the method before improvement. Even in the Japanese clinical study (C07-001), a positive HAHA response was detected before eculizumab treatment and the assay may need further improvement. Furthermore, the number of patients who developed HAHA in clinical studies was limited. Therefore, the impact of HAHA induction on the pharmacokinetics of eculizumab is undefined at present. It is desirable to further increase the assay sensitivity to HAHA and establish an assay for the measurement of neutralizing HAHA to eculizumab. After the market launch, if adverse events of infusion reaction etc. which are considered associated with HAHA induction are reported or there is loss of efficacy etc., the HAHA assay should be performed as appropriate and information on HAHA should be collected and provided to the medical practice [see "4.(iii).B.(5).7) Immunogenicity and human anti-human antibodies (HAHA)"].

4.(iii) Summary of clinical efficacy and safety

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

A total of 8 clinical studies presented in the following Table 12 were submitted as evaluation data.

Table 12. Listing of PNH clinical studies submitted

	Study Number	Phase	Primary objective of study	Design	N	Duration of treatment	Primary efficacy endpoint
Japan	C07-001	II	Efficacy, safety, pharmacokinetics, and pharmacodynamics	Open-label, uncontrolled study	29	12 weeks	Change of LDH
	E07-001 (Interim report)	II	Efficacy, safety, pharmacokinetics, and pharmacodynamics	Open-label, uncontrolled study (C07-001 extension)	27	26 weeks	–
Overseas	C02-001	I	Efficacy, safety, pharmacokinetics, and pharmacodynamics	Open-label, uncontrolled study	11	12 weeks	–
	E02-001	I	Safety	Open-label, uncontrolled study (C02-001 extension)	11	52 weeks	–
	X03-001/ X03-001A	II	Safety	Open-label, uncontrolled study (E02-001 extension)	11/10	A total of 104 weeks	–
	C04-001 (TRIUMPH)	III	Efficacy and safety	Placebo-controlled, double-blind, comparative study	43 (eculizumab group) 44 (placebo group)	26 weeks	Hb stabilization, PRBC units transfused
	C04-002 (SHEPHERD)	III	Efficacy and safety	Open-label, uncontrolled study	97	52 weeks	LDH AUC
	E05-001 (Interim report)	III	Safety	Open-label, uncontrolled study (X03-001, C04-001, and C04-002 extension)	187	Up to 2 years	–

LDH: lactate dehydrogenase, PRBC: packed red blood cell

4.(iii).A.(1) Japanese phase II clinical study (5.3.5.2.6, Study C07-001 [[redacted] to [redacted]])

A multicenter, open-label, uncontrolled study was conducted at 9 centers in Japan to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of eculizumab in PNH patients aged ≥ 12 years having a GPI-deficient RBC clone (PNH type III) ≥ 10% (Target sample size of 25).

Eculizumab was to be administered by intravenous infusion over 25 to 45 minutes at a dose of 600 mg weekly for a total of 4 doses followed 1 week later by 900 mg every 2 weeks for a total of 5 doses (the duration of treatment was 12 weeks). Patients were to receive a meningococcal vaccine (serogroups "A, C, Y, and W135") at least 2 weeks prior to treatment with eculizumab.

All of 29 treated patients were included in the per protocol set (PPS) and in the efficacy, safety, pharmacokinetic, and pharmacodynamic analyses. Two patients were discontinued from the study after 10 weeks of treatment due to lack of efficacy.

The primary efficacy endpoint was the change of lactate dehydrogenase (LDH) from baseline[††] to Week 12. There was a significant reduction in LDH from baseline (median [min., max.], 1814.0 units/L (U/L) [627.8 U/L, 3642.5 U/L]) to Week 12[‡‡] (244.0 U/L [187.0 U/L, 2715.0 U/L]) ($P < 0.0001$, Wilcoxon signed-rank test).

Regarding safety, the incidence of adverse events was 96.6% (28 of 29 patients) and the incidence of adverse events for which a causal relationship to study drug could not be denied (adverse drug reactions) was 93.1% (27 of 29 patients). Adverse events occurring in at least 10.0% of patients were headache (51.7% [15 of 29 patients]), nasopharyngitis (41.4% [12 of 29 patients]), nausea (20.7% [6 of 29 patients]), diarrhoea (13.8% [4 of 29 patients]), vomiting (10.3% [3 of 29 patients]), pyrexia (10.3% [3 of 29 patients]), and eczema (10.3% [3 of 29 patients]) and adverse drug reactions occurring in at least 10.0% of patients were headache (51.7% [15 of 29 patients]), nasopharyngitis (37.9% [11 of 29 patients]), nausea (20.7% [6 of 29 patients]), vomiting (10.3% [3 of 29 patients]), pyrexia (10.3% [3 of 29 patients]), and eczema (10.3% [3 of 29 patients]).

No deaths occurred. Serious adverse events of "pyrexia and CRP increased" were reported by 1 patient and their causal relationship to study drug could not be denied.

4.(iii).A.(2) Japanese phase II clinical study (5.3.5.2.7, Study E07-001 [20 to 20 (Interim report)])

A multicenter, open-label, uncontrolled study was conducted at 9 centers in Japan to evaluate the safety, efficacy, pharmacokinetics, and pharmacodynamics of eculizumab in PNH patients who completed Study C07-001 (Target number of patients of 27).

Eculizumab was to be administered by intravenous infusion over 25 to 45 minutes at a dose of 900 mg every 2 weeks for 52 weeks (The interim report contains data up to Week 26).

†† Mean LDH over the 4 weeks prior to start of treatment
‡‡ Missing data were imputed using last observation carried forward (LOCF).

All of 27 treated patients were included in the PPS and in the efficacy, safety, pharmacokinetic, and pharmacodynamic analyses. One patient was discontinued from the study at Week 18 due to patient request.

Regarding safety, the incidence of adverse events was 100.0% (27 of 27 patients) and the incidence of adverse drug reactions was 92.6% (25 of 27 patients). Adverse events occurring in at least 10.0% of patients were nasopharyngitis (51.9% [14 of 27 patients]), headache (18.5% [5 of 27 patients]), blood ALP increased (18.5% [5 of 27 patients]), and anaemia (11.1% [3 of 27 patients]) and adverse drug reactions occurring in at least 10.0% of patients were nasopharyngitis (51.9% [14 of 27 patients]), headache (18.5% [5 of 27 patients]), and blood ALP increased (18.5% [5 of 27 patients]).

No deaths occurred. Serious adverse events reported were "sepsis, cellulitis, skin disorder, and acute renal failure" in 1 patient, "anaemia" in 1 patient, "pyrexia and herpes simplex infection" in 1 patient, and "bronchitis" in 1 patient and a causal relationship to study drug could not be denied for all events except for anaemia.

Efficacy, pharmacokinetic, and pharmacodynamic evaluations are not planned for the interim report and the final report will be complete in June 2011.

4.(iii).A.(3) Foreign phase I clinical study (5.3.5.2.1, Study C02-001 [May 2002 to January 2003]; *N Engl J Med*. 2004;350:552-558.)

A multicenter, open-label, uncontrolled study was conducted at 2 centers overseas to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of eculizumab in PNH patients who were at least 18 years of age and had a GPI-deficient RBC clone (PNH type III) ≥ 10% (Target number of patients of 10).

Eculizumab was to be administered by intravenous infusion over at least 30 minutes at a dose of 600 mg weekly for a total of 4 doses followed 1 week later by 900 mg every 2 weeks for a total of 4 doses (the duration of treatment was 10 weeks). Patients received a meningococcal vaccine (serogroups "A and C") at least 2 weeks prior to treatment with eculizumab.

All of 11 treated patients were included in the PPS and in the safety, pharmacokinetic, and pharmacodynamic analyses. None of the patients was discontinued from the study.

Regarding safety,[§§] the incidence of adverse events was 100.0% (11 of 11 patients). Adverse events occurring in at least 2 patients were headache and upper respiratory tract infection (3 patients each) and

§§ The causal relationship of an adverse event to study drug was assessed on a 3-point scale (unlikely, possible, probable).

dizziness, nasal congestion, chest pain, influenza-like symptoms, chills, insomnia, arthralgia, and nausea (2 patients each).

No deaths occurred. Serious adverse events reported were "chest infection" in 1 patient and "nausea, vomiting, headache, dizziness, and shivering" in 1 patient.

4.(iii).A.(4) Foreign phase I clinical study (5.3.5.2.2, Study E02-001 [August 2002 to December 2003]; *Blood*. 2007;110:4123-4128, *Blood*. 2005;106:2559-2565.)

A multicenter, open-label, uncontrolled study was conducted at 2 centers overseas to evaluate the safety and tolerability of eculizumab in PNH patients who completed Study C02-001 (Target number of patients of 11).

Eculizumab was to be administered by intravenous infusion over at least 30 minutes at a dose of 900 mg every 2 weeks for 52 weeks.

All of 11 treated patients were included in the safety analysis population. None of the patients was discontinued from the study.

Regarding safety,[***] the incidence of adverse events was 100.0% (11 of 11 patients). Adverse events occurring in at least 2 patients are presented in Table 13.

Table 13. Adverse events occurring in at least 2 patients

Adverse event	Incidence	N	Adverse event	Incidence	N	Adverse event	Incidence	N
Overall	100.0%	11	Abdominal pain	18.2%	2	Myalgia	18.2%	2
Throat sore	36.4%	4	Constipation	18.2%	2	Nasal congestion	18.2%	2
Influenza-like symptoms	36.4%	4	Diarrhoea	18.2%	2	Loose stools	18.2%	2
Upper respiratory tract infection	27.3%	3	Feeling cold	18.2%	2	Throat pain	18.2%	2
Nausea	27.3%	3	Herpes simplex	18.2%	2	Throat tightness	18.2%	2
Contusion	27.3%	3	Inflicted injury	18.2%	2	Fatigue	18.2%	2
Cough	27.3%	3	Lethargy	18.2%	2	Vomiting	18.2%	2
Pain	27.3%	3	Lower respiratory tract infection	18.2%	2			

n = 11

No deaths occurred. Serious adverse events of "extravascular haemolysis, viral syndrome, and neutropenia" were reported by 1 patient.

4.(iii).A.(5) Foreign phase II clinical studies (5.3.5.2.3, Studies X03-001 and X03-001A [August 2003 to December 2005]; *Haematologica*. 2005;90:ECR40.)

Study X03-001 was a multicenter, open-label, uncontrolled study conducted at 2 centers overseas to evaluate the safety and tolerability of eculizumab in PNH patients who completed Study E02-001. PNH

[***] The causal relationship of an adverse event to study drug was assessed on a 3-point scale (unlikely, possible, probable).

patients who completed Study X03-001 were to participate in Study X03-001A.

Eculizumab was to be administered by intravenous infusion over at least 30 minutes at a dose of 900 mg every 2 weeks for a total of 104 weeks (52 weeks for Study X03-001; 52 weeks for Study X03-001A). Patients received a meningococcal vaccine (serogroups "C" or "A, C, Y, and W135").

A total of 11 treated patients in Study X03-001 and a total of 10 treated patients in Study X03-001A were included in the safety analysis. One patient was discontinued from Study X03-001 at about Week 38 due to patient request. None of the patients was discontinued from Study X03-001A.

Regarding safety,[†††] the incidence of adverse events was 100.0% (11 of 11 patients) in Study X03-001 and the incidence of adverse events was 90.0% (9 of 10 patients) and the incidence of adverse drug reactions was 20.0% (2 of 10 patients) in Study X03-001A. Adverse events occurring in at least 2 patients in Study X03-001 are presented in Table 14.

Table 14. Adverse events occurring in at least 2 patients in Study X03-001

Adverse event	Incidence	N	Adverse event	Incidence	N	Adverse event	Incidence	N
Overall	100.0%	11	Headache	27.3%	3	Viral infection	18.2%	2
Fatigue	45.5%	5	Dyspnoea	27.3%	3	Contusion	18.2%	2
Lower respiratory tract infection	36.4%	4	Nasal congestion	27.3%	3	Arthralgia	18.2%	2
Pain in extremity	36.4%	4	Abdominal pain	18.2%	2	Dizziness	18.2%	2
Pharyngolaryngeal pain	36.4%	4	Nausea	18.2%	2	Insomnia	18.2%	2
Abdominal discomfort	27.3%	3	Lethargy	18.2%	2	Epistaxis	18.2%	2
Diarrhoea	27.3%	3	Cystitis	18.2%	2	Rhinitis	18.2%	2
Influenza	27.3%	3	Upper respiratory tract infection	18.2%	2	Hypertension	18.2%	2
Nasopharyngitis	27.3%	3						

n = 11

Adverse events occurring in at least 2 patients in Study X03-001A were pharyngolaryngeal pain (40.0% [4 of 10 patients]), nasopharyngitis (30.0% [3 of 10 patients]), pyrexia (20.0% [2 of 10 patients]), lower respiratory tract infection (20.0% [2 of 10 patients]), and viral infection (20.0% [2 of 10 patients]) and there were no adverse drug reactions reported by ≥ 2 patients.

No deaths occurred. Serious adverse events reported were "abscess limb and infected left thumb" in 1 patient in Study X03-001 and "pyrexia" in 1 patient, "viral infection," in 1 patient, and "urinary tract infection" in 1 patient in Study X03-001A and a causal relationship to study drug was denied only for "viral infection" observed in Study X03-001A.

[†††] While the causal relationship of an adverse event to study drug was assessed on a 3-point scale (unlikely, possible, probable) in Study X03-001, the causal relationship of an adverse event to study drug was assessed on a 4-point scale (unrelated, possible, probable, definite) in Study X03-001A.

4.(iii).A.(6) Foreign phase III clinical study (5.3.5.1.1, Study C04-001 [TRIUMPH] [August 2004 to December 2005]; *Br J Haematol.* 2008;142:263-272, *N Engl J Med.* 2006;355:1233-1243.)

A multicenter, randomized, placebo-controlled, double-blind, comparative study was conducted at 34 centers overseas to evaluate the efficacy and safety of eculizumab in PNH patients who were at least 18 years of age and had a GPI-deficient RBC clone (PNH type III) ≥ 10% (Target number of patients of 75).

Eculizumab or placebo was to be administered by intravenous infusion over 25 to 45 minutes at a dose of 600 mg weekly for a total of 4 doses, followed by 900 mg 1 week later, and then 900 mg every 2 weeks for a total of 26 weeks. Patients received a meningococcal vaccine (serogroups "C," "A and C" or "A, C, Y, and W135") at least 2 weeks prior to treatment with eculizumab or placebo.

All of 87 treated patients (44 patients in the placebo group, 43 patients in the eculizumab group) were included in the intent to treat population and in the efficacy and safety analyses. Two patients in the eculizumab group were discontinued from the study due to an adverse event or patient request and 10 patients in the placebo group were discontinued from the study due to lack of efficacy.

The co-primary efficacy endpoints were Hb stabilization[‡‡‡] and the number of packed red blood cell (PRBC) units transfused. Hb stabilization was achieved in 0.0% of the placebo group (0 of 44 patients) compared with 48.8% of the eculizumab group (21 of 43 patients) and there was a significant difference between the groups ($P < 0.001$, Fisher's exact test). Ten units [2 units, 21 units] (median [min., max.]) of PRBCs were administered in the placebo group compared with 0 units [0 unit, 16 units] in the eculizumab group and there was a significant difference between the groups ($P < 0.001$, Wilcoxon's rank sum test).

Regarding safety, adverse events occurred in 90.9% of the placebo group (40 of 44 patients) and 100.0% of the eculizumab group (43 of 43 patients). Adverse drug reactions occurred in 25.0% of the placebo group (11 of 44 patients) and 55.8% of the eculizumab group (24 of 43 patients). Adverse events occurring in at least 10.0% of patients in either group are presented in Table 15. Adverse drug reactions occurring in at least 10.0% of patients in either group were headache only and the incidence of headache as an adverse drug reaction was 4.5% (2 of 44 patients) in the placebo group and 32.6% (14 of 43 patients) in the eculizumab group.

‡‡‡ Each patient underwent an initial observation period to identify the Hb concentration that necessitated RBC transfusion (the set-point). To achieve Hb stabilization, a patient had to maintain an Hb concentration above the Hb set-point and avoid any RBC transfusion for the entire treatment period.

Table 15. Adverse events occurring in at least 10.0% of patients in either group

Adverse event	Placebo (N = 44)		Eculizumab (N = 43)	
	Incidence	N	Incidence	N
Overall	90.9%	40	100.0%	43
Headache	27.3%	12	44.2%	19
Nasopharyngitis	18.2%	8	23.3%	10
Back pain	9.1%	4	18.6%	8
Nausea	11.4%	5	16.3%	7
Upper respiratory tract infection	22.7%	10	14.0%	6
Cough	9.1%	4	11.6%	5
Fatigue	2.3%	1	11.6%	5
Diarrhoea	11.4%	5	9.3%	4
Arthralgia	11.4%	5	7.0%	3
Abdominal pain	11.4%	5	4.7%	2
Dizziness	11.4%	5	4.7%	2
Vomiting	11.4%	5	4.7%	2
Viral infection	11.4%	5	2.3%	1

No deaths occurred. Serious adverse events occurred in 20.5% of the placebo group (9 of 44 patients) and 9.3% of the eculizumab group (4 of 43 patients), which included "exacerbation of PNH" (3 patients) and "urinary tract infection and central line infection," "exacerbation of PNH, anaemia, and pyrexia," "neutropenia," "neutropenia, cellulitis, and folliculitis," "haemolysis and upper respiratory tract infection," and "viral infection" (1 patient each) in the placebo group and "exacerbation of PNH," "renal colic," "prolapsed lumbosacral disc," and "α-Streptococcal bacteraemia" (1 patient each) in the eculizumab group and a causal relationship to study drug could not be denied only for pyrexia in the placebo group.

4.(iii).A.(7) Foreign phase III clinical study (5.3.5.2.4, Study C04-002 [SHEPHERD] [December 2004 to October 2006]; *Blood*. 2008;111:1840-1847, *Br J Haematol*. 2008;142:263-272.)

A multicenter, open-label, uncontrolled study was conducted at 33 centers overseas to evaluate the safety and efficacy of eculizumab in PNH patients who were at least 18 years of age and had a GPI-deficient RBC clone (PNH type III) ≥ 10% (Target number of patients of 85).

Eculizumab was to be administered by intravenous infusion over 25 to 45 minutes at a dose of 600 mg weekly for a total of 4 doses, followed by 900 mg 1 week later, and then 900 mg every 2 weeks for a total of 52 weeks. Patients received a meningococcal vaccine (serogroups "C," "A and C," or "A, C, Y, and W135") at least 2 weeks prior to treatment with eculizumab.

All of 97 treated patients were included in the PPS and in the efficacy and safety analyses. One patient was discontinued from the study because the patient died due to an adverse event (brain herniation) at Week 4.

The primary efficacy endpoint was LDH area under the curve (AUC) from baseline to Week 52 (LDH AUC) and the change in the LDH AUC[§§§] (median [min., max.]) was -632263.5 U/L × day [-1788823.5 U/L × day, -74498.0 U/L × day], which was significantly different from zero ($P < 0.001$, Wilcoxon signed rank test).

Regarding safety, the incidence of adverse events was 97.9% (95 of 97 patients) and the incidence of adverse drug reactions was 64.9% (63 of 97 patients). Adverse events occurring in at least 10.0% of patients are presented in Table 16. Adverse drug reactions occurring in at least 10.0% of patients were headache only (42.3% [41 of 97 patients]).

Table 16. Adverse events occurring in at least 10.0% of patients

Adverse event	Incidence	N	Adverse event	Incidence	N	Adverse event	Incidence	N
Overall	97.9%	95	Pyrexia	19.6%	19	Arthralgia	12.4%	12
Headache	52.6%	51	Back pain	15.5%	15	Abdominal pain	11.3%	11
Nasopharyngitis	32.0%	31	Dizziness	14.4%	14	Myalgia	10.3%	10
Upper respiratory tract infection	29.9%	29	Urinary tract infection	13.4%	13	Vomiting	10.3%	10
Nausea	20.6%	20	Diarrhoea	12.4%	12			

n = 97

One patient with "brain herniation" died, but its causal relationship to study drug was denied. The incidence of serious adverse events was 19.6% (19 of 97 patients) and serious adverse events occurring in at least 2 patients were anaemia (4 patients), pyrexia (3 patients), haemolysis (2 patients), and headache (2 patients). Among the observed serious adverse events, a causal relationship to study drug could not be denied for pyrexia (2 patients) and abdominal distension, renal impairment, headache, anxiety, cholangitis, and viral infection (1 patient each).

4.(iii).A.(8) Foreign phase III clinical study (5.3.5.2.5, Study E05-001 [May 2005 to March 2006 (Interim report)]; *Blood*. 2007;110:4123-4128.)

An open-label, uncontrolled study was conducted at 33 centers overseas to evaluate the safety of eculizumab in PNH patients who completed the TRIUMPH study, the SHEPHERD study, or Study X03-001A[****] (Target number of patients was not specified [up to 170 patients]).

Patients who completed the SHEPHERD study or Study X03-001 were to receive 900 mg of eculizumab every 2 weeks via 25 to 45 minute intravenous infusion. On the other hand, study drug was to be administered by intravenous infusion over 25 to 45 minutes to patients who completed the TRIUMPH study as follows: placebo-treated patients were to receive 600 mg of blinded eculizumab weekly for a total of 4 doses followed 1 week later by 900 mg of open-label eculizumab every 2 weeks; and eculizumab-treated patients were to receive 900 mg of blinded eculizumab in Week 1 and Week 3 and blinded placebo in Week 2 and Week 4 followed 1 week later by 900 mg of open-label eculizumab

§§§ The LDH AUC from baseline to 52 weeks calculated by the trapezoidal rule minus the baseline LDH AUC calculated by assuming no change in LDH from baseline through 52 weeks

**** TRIUMPH patients who had discontinued receiving study drug before Week 26 were also eligible, if their data up to Week 26 had been evaluated for efficacy and safety.

every 2 weeks. The duration of treatment was up to 2 years. Patients received a meningococcal vaccine (serogroups "A and C" or "A, C, Y, and W135") as appropriate.

All of 96 treated patients were included in the PPS and in the safety analysis (at the time of interim analysis in March 2006, the mean duration of treatment was 5.7 ± 1.9 months). None of the patients was discontinued from the study.

Regarding safety, the incidence of adverse events was 89.6% (86 of 96 patients) and the incidence of adverse drug reactions was 38.5% (37 of 96 patients). Adverse events occurring in at least 10.0% of patients are presented in Table 17. Adverse drug reactions occurring in at least 10.0% of patients were headache only (14.5% [14 of 96 patients]).

Table 17. Adverse events occurring in at least 10.0% of patients

Adverse event	Incidence	N	Adverse event	Incidence	N	Adverse event	Incidence	N
Overall	89.6%	86	Upper respiratory tract infection	15.6%	15	Cough	10.4%	10
Headache	30.2%	29	Diarrhoea	12.5%	12	Nausea	10.4%	10
Nasopharyngitis	30.2%	29	Arthralgia	10.4%	10			

No deaths occurred. The incidence of serious adverse events was 9.4% (9 of 96 patients) and serious adverse events occurring in at least 2 patients were cellulitis (2 patients), infection (2 patients), and viral infection (2 patients). Among the observed serious adverse events, a causal relationship to study drug could not be denied for cellulitis, infection, viral infection, haemophilus infection, septic shock, and headache (1 patient each).

The final report will be submitted in the [redacted] quarter of 20[redacted].

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

PMDA's review focused on the following points.

4.(iii).B.(1) Clinical positioning of eculizumab in PNH treatment

The applicant explained the pathology and treatment of PNH and the clinical positioning of eculizumab as follows:

It has been reported that in PNH patients, hemolysis results in symptoms of anaemia requiring blood transfusions, fatigue, hemoglobinuria, and recurrent abdominal pain, etc. and furthermore, serious events associated with pulmonary hypertension, renal failure, and thromboembolism (TE) occur (*Blood*. 2007;110:4123-4128, *JAMA*. 2005;293:1653-1662, *Blood*. 1981;57:83-89.). Patients with aplastic anemia (AA) or myelodysplastic syndromes (MDS) may go on to develop PNH and PNH patients often have AA or MDS as well.

Currently, the following therapies are used for PNH patients with clinically relevant hemolysis to relieve clinical symptoms considered associated with chronic intravascular hemolysis (anaemia, fatigue,

abdominal pain, TE, renal failure, pulmonary hypertension, etc.): (1) iron preparation/folic acid, (2) erythropoietin, (3) blood transfusion, (4) haptoglobin preparation, (5) corticosteroids, (6) anabolic steroids, (7) anticoagulants, (8) allogeneic hematopoietic stem cell transplantation, etc. However, the therapies (1) to (7) do not inhibit hemolysis itself. Allogeneic hematopoietic stem cell transplantation is the curative therapy for PNH, but is indicated for PNH patients with severe bone marrow failure only. Reports on the outcome of allogeneic hematopoietic stem cell transplants for PNH are shown in Table 18.

Table 18. The outcome of allogeneic hematopoietic stem cell transplants for PNH

Publication	No. of patients	Age (Median)	Mortality
***Br J Haematol*. 1999;104:392-396.**	**57**	**28**	**44% after 2 years[b)]**
***Biol Blood Marrow Transplant*. 2003;9:689-697.**	**7**	**34**	**43% at about 2-year follow-up**
***Blood*. 2005;106:3699-3709.[a)]**	**121**	**30**	**44% after 10 years**
***Thomas' Hematopoietic Cell transplantation.* 3rd ed.; 2007:1002-1006.**	**23**	**29**	**39% (the duration of follow-up is unknown)**

a) The supplemental document link at the top of the online article, at the Blood website
b) Outcome of 48 recipients of HLA-identical sibling bone marrow transplants

Since PNH patients with AA or MDS also have bone marrow failure, basically, AA or MDS is also treated simultaneously (immunosuppressants, blood transfusion, allogeneic hematopoietic stem cell transplantation, etc.).

On the other hand, since the main clinical studies of eculizumab (TRIUMPH, SHEPHERD, C07-001) have demonstrated that eculizumab reduces hemolysis, eculizumab is positioned as a first-choice drug for PNH patients. As allogeneic hematopoietic stem cell transplantation is associated with high rates of transplant-related complications and mortality, eculizumab should be considered first for PNH patients with severe bone marrow failure as well.

PMDA considers as follows:
There is no effective existing therapy for the hemolysis of PNH at present. Since the TRIUMPH study demonstrated that eculizumab stabilized Hb levels and reduced transfusion requirements by reducing hemolysis [see "4.(iii).B.(4) Efficacy"], if appropriate patients are selected, eculizumab will become an effective therapy for the hemolysis of PNH. Although allogeneic hematopoietic stem cell transplantation can be a curative therapy for PNH, not every patient can find a suitable donor and the rates of transplant-related complications and mortality are high. Thus, the decision of whether or not to perform allogeneic hematopoietic stem cell transplantation should be carefully considered, taking account of the bone marrow function and age of the patient, etc. It is understood that eculizumab may be used first also for candidates for allogeneic hematopoietic stem cell transplantation.

Meanwhile, eculizumab is not a curative therapy for PNH and continued treatment is needed to inhibit hemolysis. By protecting PNH type III RBCs against hemolysis, the percentage of PNH type III RBCs in blood increases in patients being treated with eculizumab and serious hemolysis may be induced if

eculizumab is discontinued [see "4.(iii).B.(5).8) Safety after eculizumab discontinuation"]. The effects of hemolysis inhibition by eculizumab on the development of TE and survival prognosis are unclear and moreover, eculizumab may increase the risk of infections with *Neisseria meningitidis* etc. [see "4.(iii).B.(5).4) Meningococcal infections" and "4.(iii).B.(5).5) Other infections"]. Therefore, prior to the initiation of eculizumab treatment, patients should be fully assessed for the severity of hemolysis or anaemia and complications etc. and then, eculizumab should be used only when the clinical benefits of eculizumab can be reasonably expected to outweigh the possible risks [see "4.(iii).B.(6) Indication" for the intended population].

4.(iii).B.(2) Differences in PNH between Japan and overseas

The results of a comparison of the epidemiology of PNH between Japan and the US based on the publication (*Medicine*. 2004;83:193-207.) are shown in Table 19.

Table 19. Comparison of the epidemiology of PNH between Japan and the US

		Japan	US
Gender difference in prevalence (Male/Female)		1.3	0.8
Age of onset (Median [min., max.])		45 years [10 years, 86 years]	30 years [4 years, 80 years]
Survival time after diagnosis (Median)		25.0 years	23.3 years
Preceding AA or MDS (%)	AA	37.8%	29.0%
	MDS	4.8%	5.1%
Initial symptoms (%)	Hemoglobinuria	33.5%	50.0%
	Anaemia	94.3%	88.1%
	Leukopenia/Neutropenia	7.23%	45.5%
	Thrombocytopenia	63.2%	52.3%
	Infection	3.4%	13.6%
	TE	6.2%	19.3%
Laboratory findings (Mean ± SE)	Hb level	8.2 ± 0.2 g/dL	9.7 ± 0.2 g/dL
	Reticulocyte count	78.3 ± 6.2×10^6/L	195.3 ± 13.1×10^6/L
	White blood cell count	3475.3 ± 137.5×10^6/L	4947 ± 198.6×10^6/L
	Neutrophil count	1781.6 ± 132.5×10^6/L	3005.1 ± 156.4×10^6/L
	Platelet count	96.0 ± 5.8×10^6/L	140.1 ± 8.6×10^6/L
	LDH level	1572.3 ± 91.7 U/L	2337.2 ± 405.6 U/L
Complication (%)	TE	4.3%	31.8%
	Severe infection	9.1%	18.2%
	Hematopoietic failure	36.4%	33.0%
	MDS	3.8%	3.4%
	Leukemia	2.9%	0.6%
	Renal failure	10.5%	9.1%
Cause of death (%)	TE	7.9%	42.1%
	Severe infection	36.8%	36.8%
	Renal failure	18.4%	7.9%
	Haemorrhage	23.7%	10.5%
	MDS/Leukemia	15.8%	7.9%
	Cancer	5.3%	5.3%
	Unknown	0.0%	5.3%
Treatment (%)	No treatment	28.2%	5.7%
	Blood transfusion	40.2%	61.9%
	Anabolic steroids	39.7%	36.9%
	Steroids	46.9%	82.4%
	ATG/ALG	2.9%	15.3%
	Cyclosporine	8.1%	9.7%
	Erythropoietin	3.3%	6.8%
	G-CSF	7.7%	1.7%
	Anticoagulants	4.3%	26.7%
	Allogeneic hematopoietic stem cell transplantation	1.9%	8.0%

ATG: antithymocyte globulin, ALG: antilymphocyte globulin, G-CSF: granulocyte-colony stimulating factor

It has been reported that there were marked differences in the prevalences of TE and severe infection as complications between Japan and the US and the causes of death were also different, i.e. the percentages of patients who died from TE, renal failure, or haemorrhage etc. were different.

PMDA considers that as the results of this epidemiological study have indicated differences in complications and causes of death etc. between Japan and overseas, these differences should be noted when evaluating foreign clinical study data [see "4.(iii).B.(4) Efficacy" and "4.(iii).B.(5) Safety"].

4.(iii).B.(3) Data subject to evaluation

PMDA planned its review for eculizumab as follows:

For the clinical data submitted in the application, a confirmatory study in Japanese PNH patients has not been conducted. The estimated number of PNH patients in Japan is approximately 430 (Health Science Research Grants, Research Project on Intractable Diseases, Research Committee for determining the epidemiology of diseases not covered by Research Project on Treatment of Intractable Diseases, 1999 Research Results, 2000) and it is understood that it is difficult to conduct a confirmatory, double-blind comparative study in Japan alone. PNH is an acquired genetic disorder characterized by intravascular hemolysis due to a deficiency of the GPI-anchored terminal complement inhibitor CD59 and eculizumab is an anti-C5 antibody and reduces hemolysis by inhibiting C5 and blocking the formation of the terminal complement complex C5b-9. It is inferred from the pathology of the disease and the mechanism of action that eculizumab is insensitive to ethnic factors and is expected to have similar effects also in Japanese PNH patients.

Therefore, PMDA decided to position the TRIUMPH study, which is a foreign randomized, placebo-controlled, double-blind, comparative study, as the pivotal study and use the SHEPHERD study, which is an open-label, uncontrolled, phase III study enrolling a broader range of PNH patients than in the TRIUMPH study and Study C07-001, which is a Japanese open-label, uncontrolled, phase II study, as supporting efficacy and safety data, for evaluations. However, when evaluating the efficacy and safety of eculizumab in Japanese patients by comparing the results from the Japanese clinical study (C07-001) with the results from the foreign clinical studies (TRIUMPH and SHEPHERD), epidemiological differences in PNH [see "4.(iii).B.(2) Differences in PNH between Japan and overseas"] and differences in patient background etc. among the studies need to be fully taken into consideration and the following reviews were conducted [see "4.(iii).B.(4) Efficacy" and "4.(iii).B.(5) Safety"].

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

As a result of the following reviews, PMDA considers that although the effects of eculizumab on the development of TE, which is a cause of death and is regarded as a serious problem in PNH patients, and survival prognosis etc. are undefined, as eculizumab has been shown to reduce hemolysis, if appropriate

patients are selected, the clinical benefits of inhibition of decrease in Hb levels and reductions in transfusion requirements resulting from hemolysis inhibition by eculizumab can be expected. A final conclusion on the efficacy of eculizumab will be made, taking account of comments from the Expert Discussion.

4.(iii).B.(4).1) Efficacy endpoints

As the primary endpoints for the main clinical studies, "Hb stabilization" and "the number of PRBC units transfused" for the TRIUMPH study, "LDH AUC" from baseline to Week 52 for the SHEPHERD study, and "change of LDH" from baseline to Week 12 for Study C07-001 were chosen.

PMDA asked the applicant to provide a rationale for the primary endpoint for each study and explain the relationship between LDH, which was used as a primary endpoint measure for the SHEPHERD study and Study C07-001, and hemolysis inhibition, taking also into account that LDH can be a non-specific marker.

The applicant responded as follows:

Hemolysis is the underlying cause of clinical symptoms of PNH and it was decided to choose an objective measure of eculizumab-induced reduction of hemolysis as the primary endpoint. Achievement of "Hb stabilization" was defined as maintenance of an Hb concentration above the Hb set-point and avoidance of any RBC transfusion for the entire treatment period (each patient underwent an initial observation period to identify the Hb concentration that necessitated RBC transfusion [the set-point]). This is considered a measure of stable anemia. "The number of PRBC units transfused" is considered a measure that can assess the need for blood transfusion objectively to some extent, because patients received transfusion if Hb was ≤ 9.0 g/dL with clinical symptoms or if Hb was ≤ 7.0 g/dL without clinical symptoms in the TRIUMPH study.

On the other hand, LDH can be used as a marker for intravascular hemolysis because LDH is released into the bloodstream during the hemolysis of erythrocytes and LDH is considered a measure that can assess the reduction of hemolysis by eculizumab. Although LDH may be elevated due to other tissue damage or bone marrow failure associated with MDS etc., whether or not an elevated LDH is associated with hemolysis can be determined by checking for increased free Hb, decreased haptoglobin, and decreased PNH RBCs. In clinical studies, since treatment with eculizumab resulted in lowering of LDH levels with decreased free Hb, increased haptoglobin, and increased PNH RBCs, LDH isozyme analysis was not performed, but it was thought that hemolysis inhibition was related to lowering of LDH levels.

PMDA's view on the primary endpoints for the main clinical studies is as follows:

For PNH patients presenting with progressive anemia due to chronic intravascular hemolysis, hemolysis inhibition resulting in Hb stabilization and reduced transfusion requirements has clinical significance.

Therefore, choosing “Hb stabilization” and “the number of PRBC units transfused” as the primary endpoints for the TRIUMPH study was appropriate for demonstrating the clinical significance of eculizumab.

On the other hand, although PMDA understands that the applicant used “LDH AUC” and “change of LDH” chosen as the primary endpoints for the SHEPHERD study and Study C07-001, respectively, as a measure of LDH reduction due to hemolysis inhibition, because LDH levels are known to change also in various diseases, isozyme analysis should have been performed. However, elevated LDH levels in PNH patients are considered due mainly to hemolysis and in light of the relationship to changes in free Hb, haptoglobin, and PNH RBCs etc., elevated LDH levels observed in clinical studies are considered due mainly to hemolysis. Thus, taking account of the mechanism of action of eculizumab, LDH can be used as a measure that indirectly assess hemolysis inhibition. Meanwhile, since clinically significant LDH AUC and LDH changes were not defined prior to their use as the endpoints, a problem still remains as to using these as a measure of treatment effect. The efficacy data from the SHEPHERD study and Study C07-001 demonstrated reduction of hemolysis by eculizumab rather than the favourable treatment effect of eculizumab in enrolled patients with PNH.

4.(iii).B.(4).2) Efficacy evaluation in the TRIUMPH study

For the co-primary endpoints in the TRIUMPH study, the Hb stabilization rate was 0.0% (0 of 44 patients) in the placebo group and 48.8% (21 of 43 patients) in the eculizumab group ($P < 0.001$, Fisher’s exact test) and the number of PRBC units transfused (median [min., max.]) was 10 units [2 units, 21 units] in the placebo group and 0 units [0 units, 16 units] in the eculizumab group ($P < 0.001$, Wilcoxon’s rank sum test). There were significant differences between the groups for both endpoints. Hb was maintained at levels that did not necessitate blood transfusion and transfusion requirements were reduced in more patients in the eculizumab group than in the placebo group among the PNH patients enrolled into the TRIUMPH study. Therefore, PMDA concluded that the clinical significance of hemolysis inhibition by eculizumab was demonstrated. However, as only 48.8% (21 of 43 patients) of patients achieved Hb stabilization, PMDA considered that there is a possibility that adequate treatment effect was not achieved in the study population as a whole.

4.(iii).B.(4).3) Comparison of the eligibility criteria among the main clinical studies

PMDA asked the applicant to compare the eligibility criteria among the TRIUMPH study, SHEPHERD study, and Study C07-001 and explain the reasons for differences in the criteria.

The applicant responded as follows:

The main common eligibility criteria among the 3 studies are shown in Table 20, the main different eligibility criteria are shown in Table 21, and the demographics and baseline characteristics of enrolled patients are shown in Table 22.

Table 20. Main common eligibility criteria among the TRIUMPH study, SHEPHERD study, and Study C07-001

Inclusion criteria	**PNH type III RBCs ≥ 10%, LDH ≥ 1.5 times the upper limit of laboratory reference range[a)]**
Exclusion criterion	**Neutrophil count < 500/μL**

a) 103 to 223 U/L in the TRIUMPH and SHEPHERD studies; 120 to 240 U/L in Study C07-001

Table 21. Main different eligibility criteria among the TRIUMPH study, SHEPHERD study, and Study C07-001

	TRIUMPH	SHEPHERD	C07-001
Age	≥ 18 years	≥ 18 years	≥ 12 years
Transfusion	≥ 4 transfusions in the past 12 months for anemia or anemia-related symptoms	≥ 1 transfusion in the past 2 years for anemia or anemia-related symptoms or personal beliefs that precluded transfusions	≥ 1 transfusion in the past 2 years for anemia or anemia-related symptoms or personal beliefs that precluded transfusions
Platelet count	≥ 100 000/μL	≥ 30 000/μL	≥ 30 000/μL
Hb level	Pre-transfusion Hb ≤ 10.5 g/dL over the past 12 months	Not specified	Not specified

Table 22. Demographics and baseline characteristics of patients in the TRIUMPH study, SHEPHERD study, and Study C07-001

		Overseas			Japan
		TRIUMPH		SHEPHERD	C07-001
		Placebo	Eculizumab	N = 97	N = 29
		N = 44	N = 43		
Age (Mean ± SD)		**38.45 ± 13.43 years**	**42.26 ± 15.45 years**	**41.11 ± 14.40 years**	**47.40 ± 12.39 years**
Body weight (Mean ± SD)		**72.8 ± 14.04 kg**	**74.94 ± 11.69 kg**	**73.72 ± 14.29 kg**	**61.48 ± 11.32 kg**
LDH (Mean ± SD)		**2258.0 ± 1027.1 U/L**	**2199.7 ± 1033.8 U/L**	**2199.8 ± 1034.4 U/L**	**1845.1 ± 621.14 U/L**
Hb level (Mean ± SD)		**9.63 ± 1.20 g/dL**	**10.01 ± 1.20 g/dL**	**9.19 ± 1.57 g/dL**	**7.90 ± 1.67 g/dL**
PNH RBCs (Mean ± SD)		**1.26 ± 0.69 × 10^{12}/L**	**1.12 ± 0.49 × 10^{12}/L**	**1.32 ± 0.75×10^{12}/L**	**1.26 ± 0.74 × 10^{12}/L**
Percentage of PNH type III RBC clone (Mean ± SD)		**35.14 ± 18.17%**	**27.98 ± 13.26%**	**38.72 ± 21.34%**	**43.89 ± 24.01%**
Platelet count (Mean ± SD)		**157.07 ± 76.67 × 10^{9}/L**	**188.84 ± 83.33 × 10^{9}/L**	**141.36 ± 78.54 × 10^{9}/L**	**146.2 ± 12.21 × 10^{9}/L**
PNH duration (Mean ± SD)		**10.7 ± 8.75 years**	**7.19 ± 7.21 years**	**7.41 ± 6.82 years**	**10.40 ± 6.14 years**
History of AA or MDS (%)	**AA**	**27.3% (N = 12)**	**14.0% (N = 6)**	**30.9% (N = 30)**	**37.9% (N = 11)**
	MDS	**0.0% (N = 0)**	**4.7% (N = 2)**	**1.0% (N = 1)**	**6.9% (N = 2)**
No. of transfusions in the past 12 months (Mean ± SE)		**9.0 ± 0.62**	**8.5 ± 0.61**	**5.9 ± 0.60**	**8.6 ± 1.50**
No. of PRBC units transfused in the past 12 months (Mean ± SE)		**19.8 ± 1.40 units**	**19.2 ± 1.28 units**	**12.2 ± 1.26 units**	**18.0 ± 3.02 units**

It is difficult to directly compare the amount of PRBC transfused between Japan and overseas because the volume of 1 unit of PRBC is different between Japan and overseas and the volume of 1 unit of PRBC used at each trial site was not documented in clinical studies.

PMDA considers as follows:

The eligibility criteria for the SHEPHERD study and Study C07-001 were almost the same except for age. On the other hand, the eligibility criteria as to transfusion requirements prior to study entry, platelet count, and Hb level were different between these 2 studies and the TRIUMPH study. While only patients whose bone marrow was relatively spared and who were highly transfusion-dependent were eligible for the TRIUMPH study, patients with decreased bone marrow function and patients who required relatively fewer transfusions were also eligible for the SHEPHERD study and Study C07-001.

With regard to the demographics and baseline characteristics of patients enrolled into these clinical studies, it is difficult to directly compare the amount of PRBC transfused because the specification for PRBC is different between Japan and overseas and the volume of 1 unit of PRBC used at each trial site was not documented, but patients in the SHEPHERD study and Study C07-001 tended to have lower platelet counts compared with patients in the TRIUMPH study. Patients in the C07-001 study tended to be older and have lower body weight, longer PNH duration, and lower LDH and Hb levels than patients in the TRIUMPH and SHEPHERD studies.

As described above, because differences in the demographics and baseline characteristics of patients among the studies were found, PMDA decided that subgroup analyses of the main clinical studies should be performed to identify the background factors affecting the efficacy of eculizumab [see "4.(iii).B.(4).5) Background factors affecting the efficacy of eculizumab"].

4.(iii).B.(4).4) Comparison of efficacy in the main clinical studies

PMDA asked the applicant to compare and present the results of the efficacy endpoints (Hb stabilization, the number of PRBC units transfused, LDH levels over time, change of LDH, LDH AUC) in the TRIUMPH study, SHEPHERD study, and Study C07-001.

The applicant explained as follows:

The number of PRBC units transfused, LDH levels over time, change of LDH, and LDH AUC up to Week 26 are presented in Table 23. "Hb stabilization" rates could not be calculated for the SHEPHERD study and Study C07-001 because the Hb concentration that necessitated transfusion during the observation phase (the set-point) had not been measured.

PMDA's view on comparison of efficacy in the studies is as follows:

Since "Hb stabilization" rates could not be calculated for the SHEPHERD study or Study C07-001, comparison with that in the TRIUMPH study is impossible. As previously noted, it is also difficult to simply compare "the number of PRBC units transfused" because the specification for PRBC is different between Japan and overseas and the volume of 1 unit of PRBC used at each trial site was not documented. Namely, the efficacy of eculizumab in the SHEPHERD study and Study C07-001 could not be compared with that in the TRIUMPH study in terms of improvement of anemia as indicated by "Hb stabilization" or transfusion requirements as indicated by "the number of PRBC units transfused." However, the SHEPHERD study and Study C07-001 also demonstrated a reduction in LDH from baseline, which is an indirect indicator of reduction in hemolysis, and a reduction in the number of PRBC units transfused from baseline.

Table 23. Comparison of efficacy in the main clinical studies (TRIUMPH, SHEPHERD, C07-001)

		Overseas			Japan
		TRIUMPH		SHEPHERD	C07-001
		Placebo	Eculizumab		
		N = 44	N = 43	N = 97	N = 29
PRBC units transfused	12 weeks prior to start of treatment	4.5 [2.0, 15.0]	6.0 [2.0, 9.0]	2.0 [0.0, 12.0]	2.0 [0.0, 22.0]
	12 weeks after start of treatment	4.0 [0.0, 12.0]	0.0 [0.0, 8.0]	0.0 [0.0, 14.0]	0.0 [0.0, 14.0]
	26 weeks after start of treatment	10.0 [2.0, 21.0]	0.0 [0.0, 16.0]	0.0 [0.0, 26.0]	–
LDH	Baseline (U/L)	2234.5 [a), c)] [636.0, 5530.0]	2032.0 [a)] [499.0, 5962.0]	2051.0 [a)] [537.0, 5245.0]	1814.0 [b)] [627.8, 3642.5]
	Week 1 (U/L)	2089.0 [c)] [915.0, 4753.0]	621.0 [249.0, 2453.0]	580.0 [e)] [158.0, 3166.0]	542.0 [308.0, 2230.0]
	Week 12 (U/L)	2204.0 [d)] [550.0, 4682.0]	254.0 [d)] [136.0, 6067.0]	277.0 [f)] [120.0, 4147.0]	244.0 [187.0, 2715.0]
	Week 26 (U/L)	2166.5 [1183.0, 5643.0]	239.0 [d)] [142.0, 7692.0]	270.0 [g)] [98.0, 2944.0]	–
	Change at Week 12 (U/L)	145.0 [-1578.0, 3751.0]	-1739.0 [-4138.0, 105.0]	-1758.0 [f)] [-5008.0, 975.0]	-1327 [-3166.0, 436.3]
	Change at Week 26 (U/L)	57.0 [c)] [-1426.0, 1859.0]	-1840.0 [d)] [-4065.0, -300.0]	-1795.0 [g)] [-4678.0, 931.0]	–
	LDH AUC up to Week 12 (U/L·day)	4894.8 [-164 666.5, 138 509.0]	-142 387.0 [-333 776.5, -21 437.5]	-131 723.0 [-392 532.0, -20 126.0]	-107 613.6 [-238 162.8, 10 628.1]
	LDH AUC up to Week 26 (U/L·day)	–	-313 853.0 [-733 639.0, -50 767.5]	-301 837.0 [-881 797, -39 392.5]	–

Median [Min., Max.], –: Not calculable

a) Baseline LDH (Missing data were imputed from the last visit)

b) Baseline LDH was defined as mean LDH over the 4 weeks prior to start of treatment

c) N = 43

d) N = 41

e) N = 94

f) N = 95

g) N = 96

4.(iii).B.(4).5) Background factors affecting the efficacy of eculizumab

PMDA asked the applicant to explain the influences of patient background factors on the efficacy of eculizumab.

The applicant explained as follows:

Subgroup analyses by baseline levels of transfusion requirements and Hb, which are considered an indicator of hemolysis characteristic of PNH, and baseline level of platelet count, which is considered an indicator of bone marrow function, were performed to examine the influences of these patient background factors on the efficacy endpoints (Hb stabilization, the number of PRBC units transfused). The influences of age, PNH duration, and body weight, which tended to be different between Japanese and foreign clinical studies, were examined. Furthermore, in order to assess the effects of bone marrow function and the severity of PNH, the percentage of PNH type III RBCs and concurrent AA or MDS were examined.

(a) Transfusion requirements

As shown in Table 24, regardless of transfusion requirements in the prior 12 months, the Hb stabilization rate was higher and the number of PRBC units transfused was fewer in the eculizumab group than in the placebo group in the TRIUMPH study.

In the TRIUMPH study, SHEPHERD study, and Study C07-001, when patients were stratified by transfusion requirement in the prior 12 months, there was no consistent trend in the number of PRBC units transfused by transfusion requirement in the prior 12 months.

Table 24. Influence of baseline transfusion requirements on efficacy

					Transfusion requirements in the prior 12 months (Unit)			Overall
					4-14	15-25	≥ 26	
Hb stabilization[a)]	Up to Week 12	TRIUMPH	Placebo	N = 44	6.7% (1/15)	5.6% (1/18)	0.0% (0/11)	4.5% (2/44)
			Eculizumab	N = 43	100.0% (15/15)	41.2% (7/17)	63.6% (7/11)	67.4% (29/43)
	Up to Week 26	TRIUMPH	Placebo	N = 44	0.0% (0/15)	0.0% (0/18)	0.0% (0/11)	0.0% (0/44)
			Eculizumab	N = 43	80.0% (12/15)	29.4% (5/17)	36.4% (4/11)	48.8% (21/43)
PRBC units transfused[b)]	Up to Week 12	TRIUMPH	Placebo	N = 44	2.0 [0.0, 6.0] (N = 15)	4.0 [0.0, 9.0] (N = 18)	8.0 [3.0, 12.0] (N = 11)	4.0 [0.0, 12.0] (N = 44)
			Eculizumab	N = 43	0.0 [0.0, 0.0] (N = 15)	0.0 [0.0, 6.0] (N = 17)	0.0 [0.0, 9.0] (N = 11)	0.0 [0.0, 9.0] (N = 43)
		SHEPHERD		N = 97	0.0 [0.0, 8.0] (N = 62)	0.5 [0.0, 8.0] (N = 12)	2.0 [0.0, 14.0] (N = 23)	0.0 [0.0, 14.0] (N = 97)
		C07-001		N = 29	0.5 [0.0, 3.0] (N = 15)	1.0 [0.0, 12.0] (N = 4)	0.5 [0.0, 13.0] (N = 10)	0.64 [0.0, 13.0] (N = 29)
	Up to Week 26	TRIUMPH	Placebo	N = 44	6.0 [2.0, 12.0] (N = 15)	10.0 [2.0, 12.0] (N = 18)	18.0 [10.0, 20.0] (N = 11)	10.0 [2.0, 21.0] (N = 44)
			Eculizumab	N = 43	0.0 [0.0, 4.0] (N = 15)	2.0 [0.0, 15.0] (N = 17)	3.0 [0.0, 16.0] (N = 11)	0.0 [0.0, 16.0] (N = 43)
		SHEPHERD		N = 97	0.0 [0.0, 16.0] (N = 62)	0.0 [0.0, 15.0] (N = 12)	3.0 [0.0, 26.0] (N = 23)	0.0 [0.0, 26.0] (N = 97)

a) Hb stabilization rate (N)
b) Median [Min., Max.] (N)

(b) Hb levels

As shown in Table 25, regardless of Hb levels prior to study entry, the Hb stabilization rate was higher and the number of PRBC units transfused was fewer in the eculizumab group than in the placebo group in the TRIUMPH study.

In the TRIUMPH study, SHEPHERD study, and Study C07-001, when patients were stratified by baseline Hb level, there was no consistent trend in the number of PRBC units transfused by baseline Hb level.

(c) Platelet count

As shown in Table 26, regardless of platelet counts prior to study entry, the number of PRBC units transfused was fewer in the eculizumab group than in the placebo group in the TRIUMPH study. On the other hand, although there was no difference in the Hb stabilization rate between placebo- and

eculizumab-treated patients among the subgroup of patients with a baseline platelet count ≥ 50000/μL and < 100000/μL at Week 26, the Hb stabilization rate was higher in eculizumab-treated patients than in placebo-treated patients among the subgroups of patients with a baseline platelet count ≥ 100000/μL.

In the three studies, when patients were stratified by baseline platelet count, there was no consistent trend in the number of PRBC units transfused by baseline platelet count.

Table 25. Influence of baseline Hb levels on efficacy

					Hb levels prior to study entry (g/dL)				Overall
					< 7.0	≥ 7.0 to < 9.0	≥ 9.0 to < 11.0	≥ 11.0	
Hb stabilization[a)]	Up to Week 12	TRIUMPH	Placebo	N = 44	– (N = 0)	0.0% (0/13)	4.3% (1/23)	14.3% (1/7)	4.7% (2/43)
			Eculizumab	N = 43	100.0% (1/1)	50.0% (3/6)	66.7% (20/30)	83.3% (5/6)	67.4% (29/43)
	Up to Week 26	TRIUMPH	Placebo	N = 44	– (N = 0)	0.0% (0/13)	0.0% (0/23)	0.0% (0/7)	0.0% (0/43)
			Eculizumab	N = 43	100.0% (1/1)	33.3% (2/6)	43.3% (13/30)	83.3% (5/6)	48.8% (21/43)
PRBC units transfused[b)]	Up to Week 12	TRIUMPH	Placebo	N = 44	– (N = 0)	7.0 [3.0, 12.0] (N = 13)	4.0 [0.0, 9.0] (N = 23)	2.0 [0.0, 8.0] (N = 7)	4.0 [0.0, 12.0] (N = 43)
			Eculizumab	N = 43	0.0 [0.0, 0.0] (N = 1)	1.5 [0.0, 9.0] (N = 6)	0.0 [0.0, 8.0] (N = 30)	0.0 [0.0, 0.0] (N = 6)	0.0 [0.0, 9.0] (N = 43)
		SHEPHERD		N = 97	2.0 [0.0, 14.0] (N = 10)	0.0 [0.0, 9.0] (N = 33)	0.0 [0.0, 10.0] (N = 42)	0.0 [0.0, 8.0] (N = 12)	0.0 [0.0, 14.0] (N = 97)
		C07-001		N = 29	0.0 [0.0, 13.0] (N = 8)	0.0 [0.0, 12.0] (N = 15)	0.0 [0.0, 0.0] (N = 5)	0.0 [0.0, 0.0] (N = 1)	0.0 [0.0, 13.0] (N = 29)
	Up to Week 26	TRIUMPH	Placebo	N = 44	– (N = 0)	16.0 [5.0, 21.0] (N = 13)	8.0 [2.0, 20.0] (N = 23)	8.0 [6.0, 20.0] (N = 7)	10.0 [2.0, 21.0] (N = 44)
			Eculizumab	N = 43	0.0 [0.0, 0.0] (N = 1)	4.0 [0.0, 12.0] (N = 6)	1.0 [0.0, 16.0] (N = 30)	0.0 [0.0, 2.0] (N = 6)	0.0 [0.0, 16.0] (N = 43)
		SHEPHERD		N = 97	2.5 [0.0, 26.0] (N = 10)	2.0 [0.0, 19.0] (N = 33)	0.0 [0.0, 3.0] (N = 42)	0.0 [0.0, 15.0] (N = 12)	0.0 [0.0, 26.0] (N = 97)

a) Hb stabilization rate (N)
b) Median [Min., Max.] (N)

Table 26. Influence of baseline platelet counts on efficacy

					Platelet counts prior to study entry (/μL)					Overall
					< 30 000	≥ 30 000 to < 50 000	≥ 50 000 to < 100 000	≥ 100 000 to < 150 000	≥ 150 000	
Hb stabilization[a)]	Up to Week 12	TRIUMPH	Placebo	N = 44	– (N = 0)	– (N = 0)	0.0% (0/7)	0.0% (0/16)	10.5% (2/19)	4.8% (2/42)
			Eculizumab	N = 43	– (N = 0)	– (N = 0)	75.0% (3/4)	46.2% (6/13)	76.9% (20/26)	67.4% (29/43)
	Up to Week 26	TRIUMPH	Placebo	N = 44	– (N = 0)	– (N = 0)	0.0% (0/7)	0.0% (0/16)	0.0% (0/19)	0.0% (0/42)
			Eculizumab	N = 43	– (N = 0)	– (N = 0)	0.0% (0/4)	38.5% (5/13)	61.5% (16/26)	48.8% (21/43)
PRBC units transfused[b)]	Up to Week 12	TRIUMPH	Placebo	N = 44	– (N = 0)	– (N = 0)	6.0 [2.0, 8.0] (N = 7)	4.5 [2.0, 12.0] (N = 16)	3.0 [0.0, 8.0] (N = 19)	4.0 [0.0, 12.0] (N = 42)
			Eculizumab	N = 43	– (N = 0)	– (N = 0)	0.0 [0.0, 6.0] (N = 4)	2.0 [0.0, 8.0] (N = 13)	0.0 [0.0, 6.0] (N = 26)	0.0 [0.0, 9.0] (N = 43)
		SHEPHERD		N = 97	4.5 [0.0, 9.0] (N = 2)	0.0 [0.0, 6.0] (N = 6)	2.0 [0.0, 14.0] (N = 27)	0.0 [0.0, 8.0] (N = 19)	0.0 [0.0, 8.0] (N = 43)	0.0 [0.0, 14.0] (N = 97)
		C07-001		N = 29	7.5 [2.0, 13.0] (N = 2)	0.0 [0.0, 0.0] (N = 1)	5.0 [0.0, 12.0] (N = 4)	0.0 [0.0, 0.0] (N = 8)	0.0 [0.0, 3.0] (N = 14)	0.0 [0.0, 13.0] (N = 29)
	Up to Week 26	TRIUMPH	Placebo	N = 44	– (N = 0)	– (N = 0)	15.0 [6.0, 20.0] (N = 7)	11.5 [5.0, 21.0] (N = 16)	8.0 [2.0, 18.0] (N = 19)	10.0 [2.0, 21.0] (N = 42)
			Eculizumab	N = 43	– (N = 0)	– (N = 0)	4.5 [2.0, 15.0] (N = 4)	6.0 [0.0, 16.0] (N = 13)	0.0 [0.0, 12.0] (N = 26)	0.0 [0.0, 16.0] (N = 43)
		SHEPHERD		N = 97	9.5 [0.0, 19.0] (N = 2)	3.5 [0.0, 14.0] (N = 6)	2.0 [0.0, 26.0] (N = 27)	0.0 [0.0, 15.0] (N = 19)	0.0 [0.0, 16.0] (N = 43)	0.0 [0.0, 26.0] (N = 97)

a) Hb stabilization rate (N)
b) Median [Min., Max.] (N)

(d) Age and body weight

With respect to age, younger patients tended to achieve Hb stabilization and require fewer PRBC units. PMDA is currently asking the applicant about the results on the influence of body weight.

(e) Percentage of PNH type III RBCs, PNH duration, and concurrent AA or MDS

There was no consistent trend for the influence of the percentage of PNH type III RBCs, PNH duration, or concurrent AA or MDS.

PMDA's view on the association between the patient background factors and efficacy is as follows: Regardless of the patient background factors, the number of PRBC units transfused was fewer in the eculizumab group than in the placebo group in the TRIUMPH study. The Hb stabilization rate tended to decrease with higher transfusion requirement in the 1 year prior to study treatment (Table 24), which indicated the possibility that adequate effect can not be achieved in patients with higher transfusion requirements.

Patients with low baseline Hb or platelet count tended to be unlikely to achieve Hb stabilization and

transfusion avoidance (Table 25 and Table 26). There has so far been no information that there are differences in efficacy between PNH patients with and without AA or MDS.

Based on the above, although it was suggested that patients with higher baseline transfusion requirements and patients with low baseline Hb or platelet count tended to be unlikely to achieve Hb stabilization, it does not mean that treatment effect was not achieved, taking into account that the number of PRBC units transfused tended to decrease. Therefore, it is necessary to administer eculizumab to appropriate patients, taking account of clinical treatment effect and safety [see "4.(iii).B.(5) Safety"] needed for each patient, referring to the main study data.

Especially, in a patient population not included in the TRIUMPH study, reduction in hemolysis has been demonstrated, but treatment effect, e.g. Hb stabilization, has not been studied. Thus, information should continue to be collected via post-marketing surveillance etc. and should be provided to the clinical practice as appropriate.

PMDA is currently asking the applicant about the results on the influence of body weight.

4.(iii).B.(4).6) Long-term efficacy of eculizumab

LDH levels over time in the SHEPHERD study with a treatment duration of 52 weeks are shown in Table 27.

Table 27. LDH levels over time in the SHEPHERD study

Week	Week 0 (Baseline)	Week 1	Week 2	Week 4	Week 8	Week 12	Week 26	Week 52
N	97	94	97	96	95	95	96	94
LDH (U/L)	2051.0 [537.0, 5245.0]	580.0 [158.0, 3166.0]	351.0 [149.0, 1933.0]	262.5 [93.0, 1208.0]	284.0 [118.0, 3381.0]	277.0 [120.0, 4147.0]	270.0 [98.0, 2944.0]	269.0 [106.0, 2117.0]

Median [Min., Max.]

As shown in Table 27, lowering of LDH levels was sustained in the SHEPHERD study. Thus, PMDA considered that treatment with eculizumab results in sustained decrease in hemolysis.

PMDA is currently asking the applicant about LDH levels over time and transfusion requirements over time based on pooled analyses of the submitted foreign clinical studies (TRIUMPH, SHEPHERD, C02-001, E02-001, X03-001, X03-001A, E05-001).

4.(iii).B.(4).7) Lack of efficacy of eculizumab

Since treatment discontinuation due to lack of efficacy occurred in Study C07-001 only (2 patients) among the main clinical studies (TRIUMPH, SHEPHERD, C07-001), PMDA asked the applicant to explain its cause.

The applicant responded as follows:
In Study C07-001, 2 patients did not show a pharmacodynamic response as measured by LDH levels. In an *in vitro* assay using serum samples from these 2 patients, serum complement activity was not inhibited by eculizumab, but hemolytic activity was inhibited by an anti-C5 antibody that is slightly different in structure from eculizumab (ALXN-Ab). Therefore, there is a possibility that eculizumab did not bind to C5 due to a functional variation in C5, but the cause is undefined and a detailed investigation of C5 in serum from these patients will be conducted.

PMDA considers as follows:
As lack of efficacy was observed in the Japanese clinical study only, the possibility that there are differences in efficacy between Japan and overseas also can not be ruled out, but the cause is undefined and it is necessary to continue to collect information on ineffective cases via post-marketing surveillance etc. and provide the information to the clinical practice as appropriate. Except for these 2 patients, as shown in Tables 23 and 27, LDH levels were reduced by Week 1. Therefore, if LDH levels are not reduced by Week 1, whether or not to continue treatment should be considered.

As lack of efficacy has been reported from foreign post-marketing surveillance (Table 32), PMDA is currently asking the applicant about the details.

4.(iii).B.(4).8) Efficacy against TE
TE is one of the leading causes of death in PNH and thrombus formation is considered attributed to platelet activation induced by increased free Hb concentration due to intravascular hemolysis. According to a foreign single-center, retrospective study with a 6-year [0.2 years, 38 years] (median [min., max.]) follow-up of 163 PNH patients, there were 19 TE events in 511.5 patient-years in 67 patients without history of TE and not taking warfarin; and the incidence of TE in PNH was estimated to be 3.7 per 100 patient-years (*Blood*. 2003;102:3587-3591.). On the other hand, the incidence of TE in the general population was 5.04 per 10000 person-years (*Eur J Vasc Endovasc Surg*. 2003;25:1-5.). A higher incidence of TE in PNH patients has been suggested.

With regard to the effect of eculizumab on TE, 1 TE event occurred in the placebo group and 0 TE event occurred in the eculizumab group in the TRIUMPH study. The incidence of TE was 2.34 per 100 patient-years prior to the start of treatment (calculated from previous TE events in the past) and 4.38 per 100 patient-years after the start of treatment in the placebo group, compared with 5.18 per 100 patient-years prior to the start of treatment and 0.00 per 100 patient-years after the start of treatment in the eculizumab group. Based on the pooled data from eculizumab-treated patients in foreign clinical studies (TRIUMPH, SHEPHERD, C02-001, E02-001, X03-001, E05-001), the incidence of TE was 7.37 per 100 patient-years before the start of eculizumab treatment compared with 1.07 per 100 patient-years after eculizumab treatment.

On the other hand, in the Japanese study C07-001, 5 of 29 patients had previously experienced 5 TE events and the incidence of TE was 1.66 per 100 patient-years before the start of treatment, but TE did not occur in the 3-month study period.

PMDA considers as follows:
The above results were not based on studies intended to investigate the incidence of TE and the detailed background information on concurrent use of anticoagulants, etc. is unknown and the possible influences of other factors also can not be excluded. However, foreign clinical studies have suggested that treatment with eculizumab may reduce the incidence of TE. The prevention of TE in PNH patients has a significant impact on survival prognosis. On the other hand, as it has been reported that the mortality from TE as well as the incidence of TE are lower in Japanese PNH patients than in foreign PNH patients [*Medicine*. 2004;83:193-207, see "4.(iii).B.(2) Differences in PNH between Japan and overseas"], the clinical benefits obtained from the prevention of TE may be different between Japanese PNH patients and PNH patients in the US/Europe. Therefore, the information on the development of TE, concurrent use of anticoagulants and other TE risk factors, etc. should be collected via post-marketing surveillance, differences between Japan and overseas should also be investigated, and then the information should be provided to the medical practice as appropriate.

4.(iii).B.(4).9) Efficacy during an acute hemolytic crisis
Since PNH patients are known to develop an acute hemolytic crisis associated with infections or trauma, PMDA asked the applicant to explain if there is clinical experience with eculizumab during an acute hemolytic crisis and whether or not to use eculizumab during an acute hemolytic crisis.

The applicant responded as follows:
Although there were no patients who started treatment with eculizumab after the onset of an acute hemolytic crisis associated with infections or trauma in clinical studies in PNH patients, the case of a PNH patient who developed an acute hemolytic crisis after delivery and started treatment with eculizumab has been reported from the foreign marketing experience. The patient received dialysis due to acute renal failure following the acute hemolytic crisis, but LDH levels returned to normal following treatment with eculizumab and the renal function was normalized; and dialysis was discontinued. Then, the patient was discharged and received treatment with eculizumab on an outpatient basis and was lost to follow-up thereafter.

On the other hand, the cases of hemolysis associated with infections or trauma during treatment with eculizumab (breakthrough hemolysis) were investigated. In the TRIUMPH and SHEPHERD studies, a total of 2 PNH patients experienced severe hemolysis associated with trauma during treatment with eculizumab, but continued treatment. Therefore, even if a patient develops an acute hemolytic crisis during treatment with eculizumab, treatment may be continued carefully at the discretion of the

physician.

PMDA considers as follows:
Theoretically, eculizumab is expected to be effective during an acute hemolytic crisis, as with in the setting of chronic hemolysis, but there is very limited clinical experience and the efficacy and safety information is insufficient. Thus, it is difficult to recommend the use of eculizumab for treating acute hemolytic crises. However, if patients treated with eculizumab during an acute hemolytic crisis are identified after the market launch, it is important to collect information and provide information on actions to be taken in the event of an acute hemolytic crisis to the clinical practice as appropriate.

4.(iii).B.(5) Safety
As a result of the following safety reviews on comparison of the eculizumab and placebo groups in the TRIUMPH study and on long-term safety of eculizumab etc., PMDA confirmed based on the clinical study data that special attention should be paid to the possible occurrence of headache. Furthermore, as it is inferred that patients treated with eculizumab are at an increased risk for infections with encapsulated bacteria including *Neisseria meningitidis*, PMDA reviewed the issue of the risk of meningococcal infection, including its incidence in the foreign marketing experience [see "4.(iii).B.(5).4) Meningococcal infections"]. Especially, as measures against *Neisseria meningitidis* are an important issue for the safety of eculizumab, eculizumab should be used after carefully balancing the clinical benefits and the risks. The package insert should contain stringent warnings and precautions and a fully prepared safety control system is needed.

A final conclusion on the safety of eculizumab will be made, taking account of comments from the Expert Discussion.

4.(iii).B.(5).1) Safety in the eculizumab group in the TRIUMPH study
In the TRIUMPH study, adverse events reported at a ≥ 5.0% higher incidence in the eculizumab group than in the placebo group were headache, nasopharyngitis, back pain, and fatigue (Table 15). There were no particular differences in serious adverse events.

The applicant discussed that inhibition of intravascular hemolysis by eculizumab leads to reduced free Hb, which scavenges nitric oxide (NO) and increased free NO dilates blood vessels, causing headache. PMDA is currently asking the applicant to discuss nasopharyngitis, back pain, and fatigue.

PMDA considers as follows:
No serious adverse events unique to the eculizumab group were reported and although the incidences of adverse events of headache, nasopharyngitis, back pain, and fatigue tended to be higher in the eculizumab group compared with the placebo group, headache occurred as a severe event in 1 patient

each in the placebo and eculizumab groups and there were no other severe events. Thus, although attention should be paid to the possible occurrence of headache, the results of the placebo-controlled TRIUMPH study indicate that adverse events associated with eculizumab are tolerable.

4.(iii).B.(5).2) Long-term safety of eculizumab and the influences of patient background factors on safety

Adverse events occurring in ≥ 10.0% of patients in either group up to Week 12 in the TRIUMPH study, SHEPHERD study, and Study C07-001 are shown in Table 28. Adverse events occurring in ≥ 10.0% of patients in either group during the entire treatment period in pooled foreign clinical studies (TRIUMPH, SHEPHERD, C02-001, E02-001, X03-001, E05-001) are shown in Table 29. Serious adverse events occurring in at least 2 patients up to Week 12 were anemia (3.1% [3 of 97 patients]) in the SHEPHERD study only. Serious adverse events occurring in at least 2 patients during the entire treatment period in pooled foreign clinical studies (TRIUMPH, SHEPHERD, C02-001, E02-001, X03-001, E05-001) are shown in Table 30. Of the serious adverse events listed in Table 30, those for which a causal relationship to study drug could not be denied were pyrexia (2.6% [5 of 195 patients]), headache (1.5% [3 of 195 patients]), viral infection (1.0% [2 of 195 patients]), and septic shock (1.0% [2 of 195 patients]).

Table 28. Adverse events occurring in ≥ 10.0% of patients in either group up to Week 12

	TRIUMPH				SHEPHERD		C07-001	
	Placebo (N = 44)		Eculizumab (N = 43)		Eculizumab (N = 97)		Eculizumab (N = 29)	
	Incidence	N	Incidence	N	Incidence	N	Incidence	N
Overall	84.1%	37	93.0%	40	85.6%	83	96.6%	28
Headache	20.5%	9	39.5%	17	45.4%	44	51.7%	15
Nasopharyngitis	11.4%	5	18.6%	8	11.3%	11	41.4%	12
Nausea	6.8%	3	14.0%	6	11.3%	11	20.7%	6
Diarrhoea	6.8%	3	4.7%	2	6.2%	6	13.8%	4
Vomiting	6.8%	3	4.7%	2	7.2%	7	10.3%	3
Pyrexia	4.5%	2	2.3%	1	5.2%	5	10.3%	3
Eczema	0.0%	0	0.0%	0	0.0%	0	10.3%	3
Dizziness	11.4%	5	2.3%	1	6.2%	6	3.4%	1

Table 29. Adverse events occurring in ≥ 10.0% of patients in either group during the entire treatment period in foreign clinical studies (Pooled analysis)

	Placebo (N = 44)		Eculizumab (N = 195)			Placebo (N = 44)		Eculizumab (N = 195)	
	Incidence	N	Incidence	N		Incidence	N	Incidence	N
Overall	90.9%	40	99.0%	193	Dizziness	11.4%	5	15.4%	30
Headache	27.3%	12	51.3%	100	Pharyngolaryngeal pain	9.1%	4	14.4%	28
Nasopharyngitis	18.2%	8	42.1%	82	Pain in extremity	2.3%	1	14.4%	28
Upper respiratory tract infection	22.7%	10	30.8%	60	Abdominal pain	11.4%	5	12.8%	25
Nausea	11.4%	5	25.1%	49	Insomnia	6.8%	3	11.8%	23
Diarrhoea	11.4%	5	22.1%	43	Constipation	4.5%	2	11.8%	23
Back pain	9.1%	4	20.0%	39	Viral infection	11.4%	5	11.3%	22
Pyrexia	4.5%	2	16.9%	33	Urinary tract infection	9.1%	4	11.3%	22
Vomiting	11.4%	5	16.4%	32	Contusion	6.8%	3	11.3%	22
Arthralgia	9.1%	4	15.9%	31	Influenza like illness	2.3%	1	11.3%	22
Cough	9.1%	4	15.9%	31	Myalgia	2.3%	1	10.8%	21

Foreign studies: TRIUMPH, SHEPHERD, C02-001, E02-001, X03-001, and E05-001

Table 30. Serious adverse events occurring in at least 2 patients in either group during the entire treatment period in foreign clinical studies (Pooled analysis)

	Placebo (N = 44)		Eculizumab (N = 195)			Placebo (N = 44)		Eculizumab (N = 195)	
	Incidence	N	Incidence	N		Incidence	N	Incidence	N
Overall	20.5%	9	25.6%	50	Thrombocytopenia	0.0%	0	1.0%	2
Pyrexia	2.3%	1	3.6%	7	Abdominal pain	0.0%	0	1.0%	2
Viral infection	2.3%	1	2.6%	5	Cholelithiasis	0.0%	0	1.0%	2
Anaemia	2.3%	1	2.1%	4	Viral gastroenteritis	0.0%	0	1.0%	2
Headache	0.0%	0	2.1%	4	Septic shock	0.0%	0	1.0%	2
Intervertebral disc protrusion	0.0%	0	1.5%	3	Convulsion	0.0%	0	1.0%	2
PNH	6.8%	3	1.0%	2	Nephrolithiasis	0.0%	0	1.0%	2
Cellulitis	2.3%	1	1.0%	2	Acute renal failure	0.0%	0	1.0%	2
Haemolytic anaemia	0.0%	0	1.0%	2	Neutropenia	4.5%	2	0.5%	1

Foreign studies: TRIUMPH, SHEPHERD, C02-001, E02-001, X03-001, and E05-001

Since eculizumab is an anti-C5 antibody and was considered to possibly affect the immune function, the incidence of malignant tumors was investigated.

According to foreign post-marketing surveillance (March 16, 2007 to April 1, 2009), 19 cases of neoplasms benign, malignant and unspecified (incl cysts and polyps) (acute myeloid leukaemia [3], MDS [3], skin cancer [2], acute leukaemia [1], basal cell carcinoma [1], brain neoplasm [1], endometrial cancer stage I [1], hepatic neoplasm malignant [1], leukaemia [1], lung adenocarcinoma [1], lymphoma [1], pseudolymphoma [1], renal cancer [1], uterine leiomyoma [1]) were reported, but their relationship to eculizumab is undefined at present.

On the other hand, PMDA asked the applicant to explain differences in safety profile according to patient background, based on the results from the TRIUMPH study, SHEPHERD study, and Study C07-001.

The applicant responded as follows:
Although the incidences of adverse events of nasopharyngitis, headache, and eczema etc. tended to be higher in Study C07-001 than in foreign studies, these differences are considered of no clinical significance because the diagnostic criteria are different between Japan and overseas.

The influences of body weight, age, the percentage of PNH type III RBCs, and reticulocyte count at baseline as the background factors were examined. As a result, there was no clinically significant consistent trend in the incidence of adverse events.

On the other hand, with respect to gender, the incidences of adverse events of headache, nausea, back pain, and abdominal pain tended to be higher in female patients than in male patients, but its cause is unknown. Although the incidence of headache tended to be higher in patients with fewer PRBC units transfused over the 1 year prior to the start of treatment, patients with lower baseline Hb, patients with

lower baseline platelet counts, and patients with AA or MDS, the results were inconsistent across the studies.

PMDA's view on adverse events associated with eculizumab is as follows:
The safety data up to Week 12 from the Japanese and foreign clinical studies in PNH patients showed that the incidence of headache was higher in the eculizumab group than in the placebo group and most of the events occurred by Week 5 (the incidence of headache in eculizumab-treated patients in the main clinical studies [TRIUMPH, SHEPHERD, C07-001] was 34.7% [68 of 169 patients] up to Week 5 and 7.7% [13 of 169 subjects] in Weeks 6-12). The events of headache were mostly mild or moderate in severity, but during the entire treatment period including the period beyond 12 weeks (C02-001, E02-001, X03-001, TRIUMPH, SHEPHERD, E05-001, C07-001), severe headache occurred at an incidence of 4.9% (11 of 224 patients) and serious headache occurred at an incidence of 1.8% (4 of 224 patients). Thus, attention should be paid to the possible occurrence of headache, especially during the early phase of treatment.

Other than headache, only pyrexia occurred at an incidence of ≥ 10.0% and was reported as a severe adverse event in at least 2 patients during the entire treatment period including the period beyond 12 weeks and serious pyrexia also occurred at an incidence of 3.6% (8 of 224 patients). Thus, like headache, pyrexia deserves attention. There were no other particular adverse events that deserve clinical attention. There have so far been no events that increased in incidence or severity with prolonged treatment with eculizumab. However, since there is limited clinical experience with long-term treatment with eculizumab and eculizumab possibly affects the immune function, it is important to collect information on events occurring during long-term treatment, such as influences of eculizumab on occurrence of malignant tumors and leukemia, after the market launch and provide the information to the clinical practice as appropriate.

On the other hand, as it is difficult to compare in details the safety of eculizumab, including the influences of patient background factors, between Japan and overseas due to the limited number of patients in clinical studies, the possibility of differences in safety profile between Japan and overseas can not be ruled out, but the submitted study data do not suggest the presence of differences that would significantly affect the tolerability of eculizumab.

Although no background factor that limits the use of eculizumab or requires careful administration has been identified, it is necessary to continue to collect information and provide the information as appropriate.

The safety data (adverse events and serious adverse events) from pooled Japanese (C07-001, E07-001) and foreign (TRIUMPH, SHEPHERD, C02-001, E02-001, X03-001, X03-001A, E05-001) clinical

studies are currently being requested.

4.(iii).B.(5).3) Foreign post-marketing data

Adverse events and serious adverse events reported in clinical studies in PNH patients (C07-001, E07-001, TRIUMPH, SHEPHERD, C02-001, E02-001, X03-001, X03-001A, E05-001) were compared with those reported from foreign post-marketing surveillance (from March 17, 2007 to April 1, 2009). The cumulative number of patients exposed to eculizumab was 281.03 patient-years in the PNH clinical studies and 1249 patient-years in the foreign post-marketing surveillance. Adverse events occurring at an incidence of ≥ 5.0 per 100 patient-years in either the clinical studies or foreign post-marketing surveillance are shown in Table 31 and serious adverse events occurring at an incidence of ≥ 1.0 per 100 patient-years in either the clinical studies or foreign post-marketing surveillance are shown in Table 32. No new safety issues were identified.

Table 31. Adverse events occurring at an incidence of ≥ 5.0 per 100 patient-years in either clinical studies or foreign post-marketing surveillance

Adverse event	Clinical studies		Foreign post-marketing surveillance		Adverse event	Clinical studies		Foreign post-marketing surveillance	
	Events per 100 patient-years	No. of events	Events per 100 patient-years	No. of events		Events per 100 patient-years	No. of events	Events per 100 patient-years	No. of events
Headache	40.0	115	19.5	244	Constipation	8.0	23	0.2	3
Nasopharyngitis	32.7	94	4.5	56	Urinary tract infection	7.6	22	1.7	21
Upper respiratory tract infection	20.8	60	0.7	9	Myalgia	7.6	22	1.0	13
Nausea	19.1	55	5.8	73	Flu-like symptoms	7.6	22	0.6	8
Diarrhoea	16.3	47	2.7	34	Contusion	7.6	22	0.6	8
Back pain	13.6	39	4.8	60	Viral infection	7.6	22	0.5	6
Pyrexia	12.5	36	6.2	77	Fatigue	7.3	21	6.6	83
Vomiting	12.2	35	3.0	37	Epistaxis	6.6	19	0.7	9
Arthralgia	11.1	32	2.6	32	Abdominal pain upper	5.6	16	1.2	15
Cough	11.1	32	1.4	18	Herpes labialis	5.6	16	0.4	5
Dizziness	10.8	31	2.6	33	Itching	5.2	15	1.2	15
Pain in extremity	10.1	29	1.8	23	Influenza	5.2	15	1.0	12
Pharyngolaryngeal pain	9.7	28	0.0	0	Hb decreased	0.0	0	9.7	121
Abdominal pain	8.7	25	3.4	42					

Table 32. Serious adverse events occurring at an incidence of ≥ 1.0 per 100 patient-years in either clinical studies or foreign post-marketing surveillance

Serious adverse event	Clinical studies		Foreign post-marketing surveillance		Serious adverse event	Clinical studies		Foreign post-marketing surveillance	
	Events per 100 patient-years	No. of events	Events per 100 patient-years	No. of events		Events per 100 patient-years	No. of events	Events per 100 patient-years	No. of events
Pyrexia	2.8	8	4.0	50	Pneumonia	0.3	1	1.0	13
Viral infection	1.7	5	0.4	5	Pain	0.3	1	1.0	12
Headache	1.4	4	3.0	38	Hb decreased	0.0	0	4.6	57
Anaemia	1.4	4	2.2	28	Fatigue	0.0	0	2.2	27
Abdominal pain	0.7	2	1.7	21	Blood LDH increased	0.0	0	1.4	17
Dyspnoea	0.3	1	1.8	22	Asthenia	0.0	0	1.3	16
Back pain	0.3	1	1.5	19	Death	0.0	0	1.2	15
Sepsis	0.3	1	1.1	14	Lack of efficacy	0.0	0	1.1	14
Urinary tract infection	0.3	1	1.1	14	Platelet count decreased	0.0	0	1.1	14

Although PMDA is currently asking the applicant for its view on the safety of eculizumab based on the data from the post-marketing surveillance, PMDA found no particular events that were reported at a markedly higher incidence in the foreign post-marketing surveillance than in the clinical studies. However, since cases of lack of efficacy have been reported overseas, the details of these cases are currently being requested.

4.(iii).B.(5).4) Meningococcal infections

(a) The risk of developing a meningococcal infection in patients treated with eculizumab

Eculizumab blocks the formation of the terminal complement complex (C5b-9). As *Neisseria meningitidis* having a polysaccharide capsule is lysed by the terminal complement complex (C5b-9), as with patients with a genetic disease, late complement component deficiency (LCCD), patients treated with eculizumab are considered susceptible to infections with *Neisseria meningitidis*. Although the risk of developing a meningococcal infection in LCCD patients differs depending on which terminal complement component (C5b-9) is deficient, it has been reported that the risk of meningococcal disease among LCCD individuals is 1400- to 10000-fold greater than that in normal individuals (*Clin Microbiol*. 1991;Rev 4:359-395, *J Pediatr*. 1989;114:260-264.). Thus, patients treated with eculizumab are also expected to have a similar level of risk.

On the other hand, the clinical development of eculizumab for non-PNH patients was initiated in 19[redacted] and a total of 716 patients unvaccinated against *Neisseria meningitidis* received eculizumab. In Study E99-044 in patients with idiopathic membranous glomerulonephritis, 1 patient developed meningitis caused by *Neisseria meningitidis* infection. Considering the potential risk of infection based on the mechanism of action of eculizumab, Alexion (the US) decided to require patients to be immunized with

a meningococcal vaccine prior to receiving eculizumab in subsequent clinical studies. The package inserts for eculizumab in the US/Europe state as follows: “Immunize patients with a meningococcal vaccine at least 2 weeks prior to administering the first dose of eculizumab and then revaccinate patients periodically.” and “Eculizumab is contraindicated in patients who are not currently vaccinated with a meningococcal vaccine.” However, a reduction in the risk of developing a meningococcal infection in eculizumab-treated patients immunized with a meningococcal vaccine has not been confirmed.

PMDA confirmed the following points:
· Based on its mechanism of action, eculizumab is expected to increase the risk of developing a meningococcal infection.
· The reason for requiring patients to be immunized with a meningococcal vaccine in clinical studies
· In the US/Europe where eculizumab has already been approved, the package insert requires meningococcal vaccination prior to administering eculizumab.

On the other hand, taking into account that a vaccine against *Neisseria meningitidis* is unapproved in Japan, etc., the applicant explained safety measures against meningococcal infections associated with the use of eculizumab in Japan as follows: meningococcal vaccination will not be required; the measures to reduce the risks associated with meningococcal infections, which are being implemented in foreign countries, will be employed; and a system for detecting meningococcal infections early and taking appropriate and prompt actions will be established.

Taking meningococcal infections and its safety measures seriously for the safety of eculizumab, PMDA reviewed the epidemiology of meningococcal infections, the status of meningococcal infections among patients treated with eculizumab, the effectiveness of meningococcal vaccines, and measures against meningococcal infections, as shown in (b) to (e).

(b) Epidemiology of meningococcal infections

i) Overview of meningococcal infections

The applicant explained the risk factors, clinical findings, and treatments of meningococcal infections as follows:
LCCD is known as a definitive risk factor for meningococcal infections and other risk factors include the carriage of *Neisseria meningitidis*, children at ≤ 4 years of age, and people in communal living settings at high risk of contagion.

Clinical findings of meningococcal infection include pyrexia, headache, photophobia, nuchal rigidity, mental status changes, convulsion, nausea, vomiting, and purpura/petechiae and usually, these symptoms occur acutely. Purpura/petechiae deserves attention because systemic manifestations of meningitis associated with high fatality rates, e.g. fulminant meningococcal sepsis accompanied by

hypotension, shock, and multi-organ failure, occur.

Regarding treatments, although a definitive diagnosis of meningococcal infection is made with blood/cerebrospinal fluid culture, as meningococcal infection can progress rapidly, it is important to start administering a third-generation cephem antibiotic soon after the onset of symptoms ahead of test results, if meningococcal infection is suspected. Although *Neisseria meningitidis* is generally highly susceptible to antibiotics, the fatality rate for meningococcal meningitis is as high as 10% (*IASR*. 2005;26:33-34.), and if patients respond to treatment, 10% to 15% of survivors will be left with serious sequelae.

With regard to the outcomes of meningococcal infections according to serogroup, it has been reported that the fatality rate by serogroup was 7.3% (3 of 41 patients) for serogroup B, 10.5% (2 of 19 patients) for serogroup C, and 0.0% (0 of 6 patients) for serogroup W135 in Israel (*Infection*. 1999;27:261-264.) and 11% for serogroup B, 12% for serogroup C, 17% for serogroup Y, and 8% for serogroup W135 in Sweden (*Scand J Infect Dis*. 2008;40:734-744.). No trend towards marked differences in the fatality rate according to serogroup was observed and adequate attention should be paid to all serogroups.

The extent of the risk of infection with *Neisseria meningitidis* and the incidence and prognosis of meningococcal infection, etc., in patients treated with eculizumab are undefined.

ii) Differences in meningococcal infections between Japan and overseas

The applicant explained differences in the meningococcal carriage rate, the incidence of meningococcal disease, and meningococcal serogroups, etc. between Japan and overseas as follows:

The meningococcal carriage rate among healthy adults has been estimated to be 0.64% in Japan, which has been reported to be lower than those in foreign countries (16.7% in the UK, 9.6% in Norway, 16% in Israel) (*J Med Microbiol*. 2004;53:657-662, *Lancet*. 2002;359:1829-1831, *Epidemiol Infect*. 1999; 122:51-57, *J Clin Microbiol*. 1994; 32: 323-330.).

In Japan, more than 4000 cases of meningococcal infections were reported in around 1945, which was reduced to less than 100 cases per year after 1969 and then to less than 10 cases per year in 1990s. After the enforcement of the Infectious Diseases Control Law in 1999, 8 to 22 cases of meningococcal infections occurred annually. According to a survey conducted from April 1999 to December 2004, there were 82 cases of meningococcal infections, including 8 fatal cases (*IASR*. 2005;26:33-34.), indicating that the fatality rate is about 10%. On the other hand, according to an US epidemiological surveillance, the annual incidence decreased from 1.3/100,000 population in 1989 to 0.9/100,000 population in 1991 and increased from 0.8/100,000 population in 1992 to 1.0/100,000 population in 1996 and then the annual incidence was 0.8/100,000 population in 1997 and 0.9/100,000 population in 1998 (*J Infect Dis*. 1999;180:1894-1901.), and it has been suggested that the case-fatality rate is

approximately 10% (*Emerg Infect Dis*. 2003;9:355-361.).

With respect to meningococcal serogroups, the serogroups of isolates for 182 cases collected between 1974 and 2003 in Japan were reported to be B (56.5%), Y (21.4%), W135 (0.5%), and unknown (21.4%) (*IASR*. 2005;26:36-37.) and the serogroups of isolates for 82 cases collected between April 1999 and December 2004 were reported to be B (26.8%), Y (18.3%), A (3.7%), C (1.2%), and unknown (50.0%) (*IASR* 26: 33-34, 2005). The serogroups of isolates for 807 cases collected between 1992 and 1996 in the US were C (35%), B (32%), and Y (26%) and the proportion of meningococcal cases due to serogroup Y tended to increase from 10.6% in 1992 to 32.6% in 1996 (*J Infect Dis*. 1999;180: 1894-1901.).

As shown in the above, the carriage rate, incidence, and serogroups differed from region to region and from period to period.

The information on the carriage of *Neisseria meningitidis* was not collected in clinical studies of eculizumab in PNH patients. Also in the foreign marketing experience, patients have not been tested for meningococcal carriage prior to receiving eculizumab and the information on the carriage of *Neisseria meningitidis* is not available.

There is no report suggesting that the carriage of *Neisseria meningitidis* in PNH patients is different from that in the general population.

Based on i) and ii), PMDA considers as follows:
Although it is understood that based on the presented reports, the meningococcal carriage rate is lower and the incidence of meningococcal disease is expected to be lower in the general population of Japan compared with foreign countries, as *Neisseria meningitidis* is transmitted easily by droplets from the upper respiratory tract of carriers, the risk of developing a meningococcal infection in patients treated with eculizumab is an important issue also in Japan where the carriage rate is low. Since the clinical course of meningococcal infection is generally rapid with a high fatality rate of around 10% and the rate of sequelae is also high, adequate caution and measures against meningococcal infections are needed.

(c) The occurrence and course of meningococcal infections in clinical studies and foreign marketing experience

The applicant explained the occurrence of meningococcal infections in clinical studies and marketing experience of eculizumab as follows:
Among a total of 911 patients treated with eculizumab in clinical studies up to [redacted], 3 patients developed a meningococcal infection. The cumulative number of patients exposed to eculizumab from the market launch to [redacted] overseas was estimated to be 1030 patient-years and 6 cases of

meningococcal infections were reported (Periodic safety update report from [redacted], 20[redacted] to [redacted], 20[redacted]). Meningococcal infections reported in patients treated with eculizumab are outlined in Table 33.

PMDA considers as follows:
Among the patients who developed a meningococcal infection, all patients except for 1 patient with idiopathic membranous glomerulonephritis had been vaccinated with meningococcal vaccine. The timing of vaccination was unknown for the 2 cases in clinical studies. Among the 6 cases reported from the marketing experience, 4 cases were caused by serogroup B, which was not covered by the vaccine, and the remaining 2 cases were caused by serogroup Y or C in spite of vaccination with a tetravalent (serogroups A, C, Y, and W135) vaccine, indicating that vaccination can not completely protect against the development of meningococcal infection. However, in the cases of a 2[redacted]-year-old woman in the US with serogroup Y meningococcal disease and a 3[redacted]-year-old man in the UK with serogroup C meningococcal disease, the disease developed shortly (i.e. 1 month) after revaccination 3 years after the first vaccination and 27 months after vaccination, respectively. Therefore, it can not clearly be concluded that vaccination is ineffective.

The protective efficacy of vaccine against meningococcal infections in patients treated with eculizumab is not adequately proven because comparison with unvaccinated patients has not been made. In the clinical studies and foreign marketing experience, patients who developed a meningococcal infection in spite of vaccination with meningococcal vaccine were reported and it was confirmed that even vaccinated patients can develop a meningococcal infection. Although most of the patients with meningococcal infection recovered following antibiotic treatment, there were patients who died or were left with sequelae and it was confirmed that the development of meningococcal infection can lead to a serious outcome.

Table 33. Patients of meningococcal infections reported in clinical studies and marketing experience

	Patient background (primary disease, country, sex, age)	Vaccine serogroups	Serogroup of infecting meningococcus	Time to onset		Event	Initial treatment (Antibiotics)	Outcome	Eculizumab was continued or not / Revaccination
				after vaccination	after eculizumab initiation				
Clinical studies	Idiopathic membranous glomerulonephritis US Female 2 years	Unvaccinated	A	—	—	Meningitis	Ceftriaxone Vancomycin Ampicillin	Recovered (with sequelae)	Unknown / Unknown
	PNH US Male 2 years	A, C, Y, W135	B	Unknown	11 months	Sepsis	Ceftriaxone Vancomycin	Recovered	Unknown / Unknown
	PNH Spain Female 5 years	A, C	B or Y or W135	Unknown	13 months	Sepsis	Ceftriaxone	Recovered	Unknown / Unknown
Marketing experience	PNH US Female 4 years	A, C, Y, W135	B	6 months	4 months	Meningitis	Ceftriaxone	Recovered	Continued / Unknown
	PNH Ireland Male 2 years	C	B	6 months	5 months	Sepsis	Cefotaxime Benzylpenicillin Gentamicin Metronidazole	Death	– / –
	PNH US Female 2 years	A, C, Y, W135	Y	3 years after the first vaccination, 1 month after revaccination	2 months	Sepsis	Ceftriaxone	Recovered	Continued / Unknown
	PNH UK Male 2 years	A, C, Y, W135	B	3 months	2 months	Infection	Ceftazidime	Recovered	Continued / Unknown
	PNH Denmark Male 2 years	C	B	12 months	9 months (36 days after eculizumab discontinuation)	Sepsis	Ceftazidime	Recovered	Discontinued / Unknown
	PNH UK Male 3 years	A, C, Y, W135	C	27 months after the first vaccination	21 months	Sepsis	Ceftriaxone	Recovered	Continued / Revaccinated

(d) Effectiveness of meningococcal vaccines

The protective efficacy of tetravalent meningococcal vaccines, which are currently used overseas, as described in the product package inserts, are summarized in Table 34.

Table 34. Efficacy rates of tetravalent meningococcal vaccines approved overseas

Brand name	Age	Efficacy rate as measured by serum bactericidal activity			
		A	C	Y	W-135
Menactra	2-3 years	57%	62%	84%	53%
	4-10 years	69%	81%	98%	69%
	11-18 years	100%	99%	98%	99%
	18-55 years	100%	99%	91%	97%
Menomune ACYW135	2-12 years	72%	58%	90%	82%
Menomune ACYW135	2-3 years	55%	30%	57%	26%
	4-10 years	48%	38%	84%	68%
	11-18 years	100%	99%	100%	99%
	18-55 years	99%	98%	97%	99%
Mencevax ACWY	2-5 years	90.9%	78.6%	100%	92.9%
	≥ 6 years	100%	99%	100%	100%

On the other hand, the applicant explained the status of development of vaccines other than the tetravalent meningococcal vaccines approved overseas as follows:

Concerning the status of development of a serogroup B meningococcal vaccine, two products, [redacted] ([redacted]) and [redacted] ([redacted]) are marketed in certain regions only (Cuba, Brazil, Chile, Argentina, New Zealand, etc.) to control and prevent strain-specific infections and a phase III clinical trial of [redacted] is currently ongoing overseas, but the details are unknown.

PMDA considers as follows:

According to a survey of 45 Russian patients with LCCD who experienced recurrent meningococcal infections followed for 3 to 8 years, 31 of the 45 patients were immunized with a tetravalent (serogroups A, C, Y, and W135) meningococcal vaccine and the survival rate was improved in vaccinees compared with non-vaccinees (*Vaccine.* 2003;21:4437-4447.). Thus, the efficacy of vaccination can be expected also in patients treated with eculizumab in whom the formation of C5b-9 is blocked, like LCCD patients. On the other hand, as described in "(b) Epidemiology of meningococcal infections ii) Differences in meningococcal infections between Japan and overseas," it is considered that serogroup B disease is most common in Japan (serogroup B accounted for 56.5% of isolates for 182 cases collected between 1974 and 2003; serogroup B accounted for 26.8% of isolates for 82 cases collected between April 1999 and December 2004; and serogroup B accounted for 32% of isolates for 807 cases collected between 1992 and 1996 in the US) and adverse events of Guillain-Barré syndrome etc., among recipients of a tetravalent meningococcal vaccine commonly used overseas have been reported (*MMWR Morb Mortal Wkly Rep*. 2006;55:1120-1124.). Therefore, the clinical benefits of vaccinating PNH patients in Japan need investigation.

(e) Measures against meningococcal infections in Japan

PMDA considers as follows:

Although meningococcal infections are manageable with appropriate and prompt diagnosis and treatment, as the disease can become serious/fatal, its diagnosis and treatment should begin as soon as

possible. Therefore, prior to the use of eculizumab, adequate information must be provided to hematologists who are likely prescribers of eculizumab and patients must be educated.

PMDA asked the applicant to explain the planned measures to reduce the risks associated with meningococcal infections.

The applicant responded as follows:
In foreign countries, meningococcal vaccination as a measure to minimize the risk of developing a meningococcal infection, early detection of a suspected case of the disease, and early treatment are emphasized and healthcare professionals and patients have been educated with information materials. Patients are required to carry a Patient Safety Card and show this card to any doctor at each visit.

After the market launch in Japan, as PNH is a rare disease, eculizumab is expected to be used at medical institutions that are equivalent in size to clinical trial institutes and such medical institutions are considered to be prepared for the diagnosis and treatment of PNH and meningococcal infections. However, if eculizumab is used at a medical institution that is not sufficiently prepared to treat meningococcal infections, the medical institution should seek cooperation in advance from its neighboring medical institution that is fully prepared for the treatment of meningococcal infections. The applicant will develop materials covering the information on meningococcal infections as well as PNH for physicians and for patients and establish a system for measures against meningococcal infections in PNH patients.

In order to call attention to meningococcal infections, the applicant will state in the warnings section of the package insert that “patients should be fully informed of meningococcal infections,” state in the contraindications section of the package insert that “eculizumab is contraindicated in patients with symptoms of meningococcal infection,” and list “patients with a history of meningococcal infection” in the careful administration section of Precautions of the package insert.

PMDA’s view on the measures against the risk of meningococcal infections is as follows:
Since the initial symptoms of meningococcal infection are largely non-specific and the disease can progress rapidly, become serious and lead to sequelae or death, adequate measures against meningococcal infections should be taken. Based on its mechanism of action, eculizumab is expected to increase the risk of infections with *Neisseria meningitidis*, patients were required to be vaccinated with meningococcal vaccine also in Study C07-001, and patients are required to be immunized with a meningococcal vaccine prior to receiving eculizumab overseas. Thus, in order to reduce the risk of meningococcal infections, meningococcal vaccination can be used as a promising measure against meningococcal infections also in Japan. However, there is currently no approved meningococcal vaccine whose efficacy and safety have been demonstrated in Japanese subjects and since i) the major

tetravalent vaccines (serogroups A, C, Y, and W135), which are currently used overseas, are expected to have limited efficacy against serogroup B disease, which has been relatively commonly reported in Japan, ii) a reduction in the risk of developing a meningococcal infection in patients treated with eculizumab has not been confirmed for any vaccine including the serogroup B vaccines which are used in certain regions, and iii) in clinical studies in PNH patients and foreign post-marketing surveillance, in spite of vaccination, meningococcal infections including those caused by the serogroups covered by the vaccine occurred, etc., even vaccinated patients can develop a meningococcal infection.

Based on the above, although vaccination can also become a measure to minimize the risks associated with meningococcal infections, considering that even vaccination can not completely protect against the disease, other feasible measures in Japan should be taken first, regardless of meningococcal vaccination status. In order to reduce the risks associated with meningococcal infections, adequate measures against meningococcal infections should be built, adequate information on the risks and benefits of eculizumab should be provided to healthcare professionals and patients, and eculizumab should be initiated after both the healthcare professional and patient understand the risks and benefits of eculizumab. It is necessary to continue to review the need for meningococcal vaccination while collecting information actively in Japan and overseas.

4.(iii).B.(5).5) Other infections

The incidences of infections up to Week 12 in the TRIUMPH study, SHEPHERD study, and Study C07-001 and during the entire study period in studies in PNH patients (C07-001, E07-001, TRIUMPH, SHEPHERD, C02-001, E02-001, X03-001, X03-001A, E05-001) are shown in Table 35.

Table 35. Incidences of infections in Japanese and foreign clinical studies

	Up to Week 12								Entire study period					
	TRIUMPH				SHEPHERD		C07-001		TRIUMPH		Foreign clinical studies		Japanese clinical studies	
	Placebo (N = 44)		Eculizumab (N = 43)		Eculizumab (N = 97)		Eculizumab (N = 29)		Placebo (N = 44)		Eculizumab (N = 195)		Eculizumab (N = 29)	
	Incidence	N	Incidence	N	Incidence	N	Incidence	N	Incidence	N	Incidence	N	Incidence	N
Infection	68.2%	30	55.8%	24	45.4%	44	62.1%	18	77.3%	34	92.8%	181	75.9%	22
Serious infection	6.8%	3	0.0%	0	1.0%	1	3.4%	1	11.4%	5	13.8%	27	10.3%	3

TRIUMPH study (study duration, 26 weeks)
Japanese clinical studies (study duration, up to 38 weeks): C07-001, E07-001 (Interim report)
Foreign clinical studies (study duration, up to 206 weeks): TRIUMPH, SHEPHERD, C02-001, E02-001, X03-001, X03-001A, and E05-001 (Interim report)

PMDA confirmed that there were no major differences in the incidence of infections between the placebo and eculizumab groups and between Japan and overseas (up to Week 12).

PMDA asked the applicant to explain about any infection that deserves special attention other than that with *Neisseria meningitidis*.

The applicant responded as follows:
Since eculizumab is a specific anti-C5 antibody and blocks the formation of the terminal complement complex C5b-9 without inhibiting the formation of an early complement component, C3b, which is essential for microbial opsonization and immune complex clearance, eculizumab is not considered to increase the risk of other common infections except for those caused by encapsulated bacteria (especially, *Neisseria meningitidis*) that are cleared by terminal complement components. This has been suggested also by clinical studies in PNH patients in which the overall incidence and severity of infections were similar between the eculizumab and placebo groups.

On the other hand, when opinions on the effect of eculizumab on the risk of infections other than those caused by *Neisseria meningitidis* were sought from an infection specialist and the investigators, they responded that the risk of infections with encapsulated bacteria, e.g. *Streptococcus pneumoniae* or *Haemophilus influenzae*, associated with eculizumab can not be denied. The frequency of occurrence of infections with encapsulated bacteria in patients with complement deficiencies differs depending on which complement is deficient and it has been reported that in patients with C5-9 deficiencies, the frequency of occurrence of *Neisseria sp.* infection was 57% (151 patients), the frequency of occurrence of *Streptococcus pneumoniae* infection was 0.8% (2 patients), and the frequency of occurrence of *Haemophilus influenzae* infection was 0% (0 patients) (*Clin Microbiol*. 1991;Rev 4:359-395.).

Even taking account of the above points, based on its mechanism of action, eculizumab may increase the risk of infections with encapsulated bacteria, e.g. *Streptococcus pneumoniae* or *Haemophilus influenzae*. Therefore, the applicant will develop materials calling attention to infections for patients and for healthcare professionals and list “patients with systemic infections” in the careful administration section of Precautions of the package insert.

PMDA considers as follows:
Although the submitted clinical study data showed no clear trend towards an increased risk of infections associated with eculizumab, the limited number of patients were studied and since eculizumab blocks the formation of the terminal complement complex acting on capsular polysaccharides, there may be a theoretical increased risk of infections with not only *Neisseria meningitidis*, but also *Streptococcus pneumoniae* and *Haemophilus influenzae*. In patients with C5b-9 deficiency, the incidence of *Streptococcus pneumoniae* or *Haemophilus influenzae* infection tended to be lower than the incidence of *Neisseria* infection, but it is difficult to completely deny an increased risk of infections with these bacteria.

Based on the above, there is no problem with listing “patients with infections” in the careful administration section of Precautions of the package insert. It is also necessary to develop materials for patients and for healthcare professionals to call attention to infections as a whole. In addition, it is

necessary to collect information on the incidence, severity, and outcome of infections via post-marketing surveillance etc. and provide the information appropriately to healthcare professionals and patients if a new finding becomes available.

4.(iii).B.(5).6) Infusion reactions

Since eculizumab is an antibody preparation, administration of eculizumab may result in infusion reactions. PMDA asked the applicant to explain how to prevent/manage infusion reactions.

The applicant responded as follows:

In clinical studies, a specific guidance on how to manage infusion reactions was not provided and infusion reactions were prevented and managed at the discretion of the physician. Mild to moderate infusion reactions were reported by 1 patient in the TRIUMPH study and 3 patients in the SHEPHERD study, which resolved following interruption of eculizumab or symptomatic treatment and then the patients were able to continue treatment with eculizumab with preventive measures taken before the administration of eculizumab.

It is recommended to slow the infusion rate (up to 5 mg/min for 600 mg doses, up to 7.5 mg/min for 900 mg doses) and administer an histamine H_1 antagonist, an histamine H_2 antagonist, or a steroid, etc. At the medical institution, patients should be monitored for at least 1 hour following the completion of the infusion or patients with an infusion reaction or a history of an infusion reaction should be monitored for at least 2 hours following the completion of the infusion to ensure safety.

PMDA considers as follows:

The information on the recommended practices for the prevention and management of infusion reactions should be provided appropriately. After the market launch, the information on the development of infusion reactions, its relationship with the infusion rate, and how infusion reactions were managed and prevented should be collected and the information should be provided to the medical practice as appropriate.

4.(iii).B.(5).7) Immunogenicity and human anti-human antibodies (HAHA)

The applicant explained the immunogenicity and HAHA induction following treatment with eculizumab as follows:

The rates of the induction of HAHA in foreign clinical studies of eculizumab in PNH and non-PNH subjects are shown in Table 36. HAHA was not detected in a Japanese clinical study C07-001 and analysis has not been performed in Study E07-001 (Interim report). The presence of neutralizing antibodies has not been determined because its assay is under development.

Table 36. HAHA response following treatment with eculizumab

	PNH clinical studies				Non-PNH clinical studies[a)]				All studies			
	Placebo		Eculizumab		Placebo		Eculizumab		Placebo		Eculizumab	
No. of patients with HAHA measurement	N = 44		N = 151		N = 206		N = 677		N = 250		N = 828	
	Incidence	N	Incidence	N	Incidence	N	Incidence	N	Incidence	N	Incidence	N
Positive HAHA response	2.3%	1	1.3%	2	5.3%	11	3.8%	26	4.8%	12	3.4%	28
Positive IgM response	–	–	0.7%	1	2.4%	5	1.0%	7	2.0%	5	1.0%	8
Positive IgG response	2.3%	1	1.3%	2	3.4%	7	3.0%	20	3.2%	8	2.0%	21
Positive IgG and IgM response	–	–	–	–	0.5%	1	0.1%	1	0.4%	1	0.1%	1

a) Clinical studies in patients with rheumatoid arthritis, idiopathic membranous glomerulonephritis, dermatomyositis, or psoriasis

Regarding safety in patients with a positive HAHA response, 1 patient each in the TRIUMPH and SHEPHERD studies developed HAHA within 26 weeks of treatment and the 1 patient in the TRIUMPH study had coagulopathy, headache, and haematoma and the 1 patient in the SHEPHERD study had pyrexia and nasopharyngitis. One patient in the placebo group in the TRIUMPH study also had a positive HAHA response, which was considered due to measurement errors or contaminants. The assay method for the measurement of HAHA has been improved and the sensitivity of the assay method used in the Japanese clinical study is higher than that used in the foreign clinical studies. As the assay reagent used in Study C07-001 will become unavailable at the end of 2010, a new assay method will be employed in January 2010.

PMDA considers as follows:

At present, the relationship between positive HAHA response and the occurrence of adverse events is unknown. After the market launch, if adverse events of infusion reactions etc. possibly related to HAHA induction occur or there is loss of efficacy of eculizumab etc., HAHA should be measured as appropriate and the information on HAHA should be collected and provided to the medical practice as appropriate.

4.(iii).B.(5).8) Safety after eculizumab discontinuation

By protecting PNH type III RBCs against intravascular hemolysis, the percentage of PNH type III RBCs increases in patients being treated with eculizumab (Based on the pooled data from the TRIUMPH and SHEPHERD studies, the percentage of PNH type III RBCs [median] was 31.7% at baseline, 46.5% at Week 8, and 51.5% at Week 26) and a serious hemolytic crisis may be induced if eculizumab is discontinued. PMDA asked the applicant to explain the clinical courses of patients who were discontinued from treatment with eculizumab and necessary measures after discontinuation.

The applicant responded as follows:

In Japanese and foreign clinical studies in PNH patients, a total of 13 patients were discontinued from eculizumab treatment due to lack of efficacy or adverse events etc. In the foreign marketing experience, 67 cases of treatment discontinuation were reported and the information after treatment discontinuation was obtained for 51 of the 67 cases. When “serious hemolysis” after treatment discontinuation is defined as a rise in LDH above the baseline level at the onset of the event and either (a) a ≥ 25%

reduction in PNH type III RBCs within 1 week of the onset of the event, (b) Hb < 5.0 g/dL or a > 4.0 g/dL reduction in Hb within 1 week of the onset of the event, (c) the occurrence of angina pectoris or TE, (d) mental status changes, or (e) a 50% increase in serum creatinine, serious hemolysis meeting this definition has not been reported among the patients who were discontinued from eculizumab treatment in the clinical studies and marketing experience.

However, as the risk of serious hemolysis can not be denied theoretically, after the market launch, patients will be monitored for at least 8 weeks after eculizumab discontinuation to detect serious hemolysis. If serious hemolysis occurs after eculizumab discontinuation, PRBC transfusion, readministration of eculizumab, and exchange transfusion etc. should be considered.

PMDA considers as follows:
Although there has so far been no patients who developed serious hemolysis meeting the applicant's definition after eculizumab discontinuation, as the risk of a serious hemolytic crisis exists theoretically, the information on the risks associated with eculizumab discontinuation and the need for monitoring patients after eculizumab discontinuation should be provided to the medical practice appropriately. Since appropriate management after eculizumab discontinuation has not been established, it is unavoidable that the patients are treated at the physician's discretion according to individual patients' symptoms. After the market launch, the information on the clinical course and management of patients after eculizumab discontinuation should be collected and the information on the risks associated with discontinuation and management should be provided to the medical practice as appropriate.

4.(iii).B.(6) Indication
The proposed indication was "paroxysmal nocturnal hemoglobinuria (PNH)."

PMDA's view on the indication for eculizumab is as follows:
The TRIUMPH study demonstrated the superiority of eculizumab over placebo for "Hb stabilization" and "the number of PRBC units transfused" and the SHEPHERD study and Study C07-001 showed reductions in LDH from baseline. The results of these studies and subgroup analyses indicate that eculizumab reduces hemolysis in PNH patients while Hb stabilization and a reduction in the number of PRBC units transfused, which are considered clinical indicators of treatment effect, have been demonstrated in the TRIUMPH study only. Therefore, although the submitted data have shown reduction in hemolysis in PNH patients, treatment effect associated with reduction in hemolysis has been demonstrated only in the TRIUMPH study population, i.e. patients who are relatively more dependent on transfusions and whose bone marrow is relatively spared.

The effects of eculizumab on the incidence of TE, which is regarded as a clinically serious problem in PNH patients, and survival prognosis have been undefined also in the TRIUMPH study and whether

reduction in hemolysis and improvement of anemia by eculizumab are related to the ultimate improvement in survival prognosis is unknown.

On the other hand, regarding safety, although there has been no serious problem in clinical studies, as the potential risks of eculizumab, an increased risk of infections with encapsulated bacteria, e.g. *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* and the risk of a serious hemolytic crisis after treatment discontinuation have been identified.

Therefore, eculizumab should be used in appropriate patients, fully examining treatment effects and potential risks, taking into account that eculizumab is palliative and improvement in survival prognosis has not been demonstrated at present.

Based on the above, the appropriate indication statement should be "reduction of hemolysis in patients with paroxysmal nocturnal hemoglobinuria" etc. and it should be stated that eculizumab is indicated for transfusion-dependent patients with a PNH type III RBC clone ≥ 10%, i.e. the patient population included in the clinical studies. The package insert should state that Hb stabilization and reductions in transfusion requirements have been demonstrated in the TRIUMPH study population and advise that eculizumab should be used only if the clinical benefits are considered to outweigh the potential risks.

Moreover, the following information should also be provided appropriately: the eligibility criteria for the TRIUMPH study; and the efficacy of eculizumab during an acute hemolytic crisis has not been demonstrated.

Since foreign extension studies suggest that eculizumab may reduce the incidence of TE, it is desirable to continue to collect information and investigate the incidence of TE, taking account of differences in PNH conditions between Japan and overseas.

The way of providing information on the intended population for eculizumab, e.g. the indication and precautions for indication of the package insert, will be finalized, taking account of comments from the Expert Discussion.

4.(iii).B.(7) Dosage and administration

The applicant explained the rationale for the dosage regimen used in clinical studies in PNH patients and how dosage and administration was established as follows:

In a study of eculizumab in patients with rheumatoid arthritis conducted in the early phase of development, although weekly administration of 8 mg/kg completely inhibited C5 activity in the sera from all patients, when the patients were switched to once every 2 weeks administration, C5 concentrations recovered in several patients. Then, considering that 35 μg/mL of eculizumab can

theoretically bind to all C5 in human serum and based on the results from clinical studies in patients with rheumatoid arthritis or idiopathic membranous glomerulonephritis etc., a serum eculizumab concentration of 35 μg/mL was chosen as a threshold for efficacy [see "4.(ii).B.(1). Relationship between serum eculizumab concentration and hemolytic activity"].

Since a simulation showed that the trough concentrations corresponding to the 8 mg/kg dose can be maintained at a fixed dose of 600 mg, Study C02-001 in PNH patients used fixed doses of eculizumab and a dosage regimen of 600 mg weekly for 4 doses followed by 900 mg every 2 weeks for the purpose of maintaining serum eculizumab concentrations sufficient to completely inhibit C5 activity during the study period. In order to determine the dosage regimen that maintains serum trough concentrations of ≥ 35 μg/mL based on the results from Study C02-001, a simulation was performed using model parameters obtained from 11 PNH patients to assess dosage regimens. Finally, the relationships between serum eculizumab concentration and hemolytic activity in the TRIUMPH study, SHEPHERD study, and Study C07-001 were assessed and dosage and administration for eculizumab was established.

PMDA's view on dosage and administration for eculizumab is as follows:
Although how dosage and administration was established is understood, even serum concentrations of eculizumab above 35 μg/mL do not sufficiently inhibit hemolysis in some patients [see "4.(ii).B..(1) Relationship between serum eculizumab concentration and hemolytic activity"] and as other dosage regimens have not been investigated in PNH patients, there is no sufficient information to determine whether the proposed dosage regimen has been optimized and the appropriateness of dosage and administration is questionable. However, since the pivotal clinical study of eculizumab in PNH patients, the TRIUMPH study, has confirmed the efficacy of eculizumab [see "4.(iii).B.(4) Efficacy"], Study C07-001 has suggested reduction in hemolysis at the same dosage regimen also in Japanese patients, and the safety profile of eculizumab is also tolerable, it is unavoidable to select the dosage regimen used in the TRIUMPH study and Study C07-001 etc.

Dosage and administration for eculizumab will be finalized, taking account of comments from the Expert Discussion.

4.(iii).B.(8) Use in children, pregnant women, and nursing mothers

4.(iii).B.(8).1) Pediatric use

The applicant explained the pediatric use of eculizumab as follows:
Although pediatric patients aged ≥ 12 years were eligible for a Japanese clinical study (C07-001), no patients aged ≥ 12 and < 18 years were enrolled into the study.

In the foreign marketing experience, 34 children were treated with eculizumab (as of August 24, 2009), including 17 PNH patients, 14 patients with atypical hemolytic uremic syndrome, 1 patient with bone

marrow transplant rejection, 1 renal transplant recipient, and 1 patient with membranoproliferative glomerulonephritis II. Adverse events reported by at least 2 patients were headache only (2 patients) and there were no major differences in the safety profile between pediatric and adult patients.

Meanwhile, for the development of eculizumab for pediatric use, a clinical study to evaluate the pharmacokinetics, pharmacodynamics, and safety of eculizumab in about 6 to 8 pediatric and adolescent patients with PNH (2-17 years) is scheduled to be initiated in the US and Europe in 2009 (Study M07-005), but there is no plan to enroll Japanese patients. Clinical studies in adolescent patients with atypical hemolytic uremic syndrome are ongoing in the US and Europe. A study in pediatric patients with atypical hemolytic uremic syndrome is also under planning and the participation of Japanese patients is under consideration.

PMDA concluded as follows:
There is very limited clinical experience with eculizumab in pediatric patients at present. Although the majority of patients are adults based on the age of onset of PNH, as there are also pediatric patients, it is preferable to develop eculizumab for Japanese pediatric patients as well.

PMDA is currently asking the applicant about the seriousness of adverse events and their causal relationship to eculizumab in the foreign post-marketing surveillance and any plan of a clinical study in Japanese pediatric patients with PNH.

4.(iii).B.(8).2) Use during pregnancy or lactation
PMDA asked the applicant to explain the use of eculizumab during pregnancy in clinical studies and foreign post-marketing surveillance.

The applicant responded as follows:
Reported pregnancies from patients on eculizumab during clinical studies and post-marketing surveillance (up to August 15, 2009) are as shown in Table 37.

Table 37. Reported pregnancies during clinical studies and post-marketing surveillance

		Actions taken and Outcome
Clinical studies	E02-004 (Rheumatoid arthritis)	The patient discontinued eculizumab treatment and elected to terminate her pregnancy.
	SHEPHERD	The patient discontinued eculizumab treatment and elected to terminate her pregnancy.
	TRIUMPH	The patient discontinued eculizumab treatment and delivered a healthy baby by cesarean section at 39 weeks of gestation.
	E05-001	The patient discontinued eculizumab treatment and delivered a healthy baby by cesarean section at 38 weeks of gestation.
	E05-001	The patient discontinued eculizumab treatment and had a normal delivery with a healthy baby at 39 weeks of gestation.
	C02-001 and E05-001	The patient continued eculizumab treatment and delivered a healthy baby at 38 weeks of gestation (probably, a normal delivery)
Post-marketing surveillance		The patient discontinued eculizumab treatment, but recommenced due to hemolysis during pregnancy and delivered healthy babies by cesarean section (twins). (The patient developed a post-partum hemorrhage due to persistent retained products of conception.)
		The patient continued eculizumab treatment and had a spontaneous abortion at 8-9 weeks of gestation.
		The patient discontinued eculizumab treatment, but recommenced at 30 weeks of gestation and delivered healthy babies by cesarean section at 36 weeks of gestation (twins).
		The patient discontinued eculizumab treatment and elected to terminate her pregnancy due to severe AA, severe thrombocytopenia, and severe neutropenia associated with Escherichia sepsis. (Autopsy revealed no fetal abnormalities and the patient underwent allogeneic bone marrow transplantation 27 days after termination of pregnancy.)
		The patient continued eculizumab treatment and had a normal delivery with a healthy baby.
		The patient continued eculizumab treatment and had a preterm cesarean delivery at 27 weeks of gestation.
		Whether eculizumab treatment was continued or not is unknown. Due to intestinal ischaemia followed by knee pain, pneumonia, septic shock, and respiratory failure, the patient underwent a cesarean section at 27 weeks of gestation, but her baby died.
		The patient continued eculizumab treatment and was in her first month of gestation as of March 2009.
		The patient discontinued eculizumab treatment and was in the first trimester as of March 2009.
		The patient discontinued eculizumab treatment, but will recommence in the third trimester. The patient was in her 7th week of gestation as of March 2009.
		The patient continued eculizumab treatment and had a spontaneous abortion.
		Whether eculizumab treatment was continued or not is unknown. The patient had a therapeutic abortion.
		The patient continued eculizumab treatment and was in her 8th to 10th week of gestation as of April 2009.
		The patient continued eculizumab treatment and had a preterm cesarean delivery at 27 weeks of gestation.

It has been reported that PNH patients who received eculizumab and low-molecular-weight heparin during the third trimester and the perinatal period and after delivery had no adverse events from Week 30 of gestation to 3 months post-partum (*Leuk Res*. 2009;33:e4-e5.).

Although it is unknown whether eculizumab is excreted into human milk, as IgG is considered to be excreted in human milk, the possibility that eculizumab is excreted into human milk can not be ruled out and in accordance with the package insert in Europe, it will be stated in the package insert that "breast-feeding should be discontinued during treatment and up to 5 months after treatment."

PMDA considers as follows:

There is very limited clinical experience with eculizumab in pregnant women. Based on the currently available information, fetal effects are unknown.

It is necessary to call attention to potential excretion in milk. Meanwhile, although the maximum $t_{1/2}$ (estimated by an analysis with a 1-compartmental model) in the TRIUMPH study, SHEPHERD study, Study E05-001, and Study C07-001 (566.9 hours [23.6 days]) indicates that eculizumab is almost completely eliminated from blood at 5 months after treatment, there is no definitive basis for 5 months of discontinuation of breast-feeding. Therefore, it is unnecessary to specify the period of discontinuation in the package insert.

Eculizumab is intended for chronic use and may be used in pregnant women or nursing mothers after the market launch. Thus, it should be advised that the information is limited as described above and eculizumab may be excreted into milk and it is necessary to collect information on the effects of eculizumab on pregnant women and fetuses and nursing mothers and babies and appropriately provide the information to the medical practice as needed.

4.(iii).B.(9) Post-marketing surveillance etc.

The applicant presented an outline of post-marketing surveillance (draft) as shown in Table 38.

Table 38. Outline of post-marketing surveillance plan (draft)

Objectives	**Detection of unknown and serious adverse drug reactions** **Long-term safety and efficacy** **Effects of eculizumab on the course of PNH (the course and prognosis etc. of the disease)**
Survey period	**8 years (≥ 3 years as a survey of long-term use)**
Planned number of cases	**All treated patients**
Target patient population	**PNH patients**
Major items to be investigated	• **Patient background (medical history [TE, others], underlying disease [AA, MDS, others], PNH duration, complications [major vascular events, hepatic impairment/renal impairment, others])** • **The status of administration of eculizumab (including the reason for discontinuation)** • **Concomitant medications (steroids, immunosuppressants, anticoagulants, others)** • **Adverse events** • **Efficacy (change of LDH, improvement in QOL [fatigue, abdominal pain, dyspnoea, dysphagia], change in Hb, the number of PRBC units transfused)** • **Clinical course up to 8 weeks after treatment discontinuation (the development of a hemolytic crisis, etc.)** • **Significant events including malignant tumors (meningococcal infection, infections leading to serious outcomes such as hospitalization and death, death, serious hemolysis after discontinuation, pregnancy, TE, malignant tumors)** **[Priority item]** • **Development of infections**

As an epidemiological study, the PNH registry is run by Alexion, the US, which will be incorporated into post-marketing surveillance after necessary modifications.

PMDA considers as follows:

Besides the above, the information regarding the following (a) to (c) should also be collected and monitoring after treatment discontinuation and the development of TE should be treated as priority items. As eculizumab is an orphan drug and there is very limited clinical experience with eculizumab in Japan, as a condition for approval, the applicant is required to conduct a post-marketing survey covering all treated patients. Post-marketing commitments will be finalized, taking account of comments from the Expert Discussion.

An overview of the global PNH registry is currently being requested.

(a) PNH type III RBC clone over time
(b) Information on HAHA
(c) Safety of eculizumab in children and pregnant women/nursing mothers

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

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

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

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

GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (Study C07-001, 5.3.5.2-6 and Study E07-001, 5.3.5.2-7). As a result, failure to operate the IRB in accordance with the SOP (in response to the reports of adverse drug reactions etc. notified by the sponsor, the appropriateness of continuing the clinical trial and amendments to the written information were reviewed through expedited review procedures) and protocol deviations (a chest X-ray had not been performed in some subjects) were found at some clinical trial sites. Furthermore, there were imperfections in the sponsor's monitoring report on the operation of the IRB regarding the above-mentioned reports of adverse drug reactions etc., but PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application dossier.

IV. Overall Evaluation

Based on the submitted data, the efficacy of eculizumab in patients with PNH has been demonstrated and its safety is acceptable in view of its observed benefits. Since eculizumab is an anti-C5 antibody and offers a new treatment for patients with PNH, it has clinical significance. PMDA considers that the points listed below need to be further reviewed.

Eculizumab may be approved if it can be concluded based on comments from the Expert Discussion that there are no particular problems.

- Data subject to evaluation
- Efficacy
- Safety
- Measures against meningococcal infections
- Indication
- Dosage and administration
- Post-marketing commitments

Review Report (2)

February 18, 2010

I. Product Submitted for Registration

[Brand name]	Soliris for Intravenous Infusion 300 mg (Note: The proposed Japanese brand name has been modified.)
[Non-proprietary name]	Eculizumab (Genetical Recombination)
[Name of applicant]	Alexion Pharma K.K.
[Date of application]	March 31, 2009

II. Content of the Review

The Expert Discussion and subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below.

The expert advisors for the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

(1) Quality

As a result of the following reviews including the questions asked to the applicant, PMDA concluded that the quality of the drug product to be marketed is adequately controlled.

(1).1) Evaluation of disulfide bond heterogeneity

Although it is understood that it is difficult to control disulfide bond variants quantitatively, PMDA asked the applicant to explain the need to control the heterogeneity of these variants, taking account of the possible effects of these variants on the safety and efficacy of eculizumab.

The applicant responded as follows:

Since disulfide bond variants are considered to be present also in the previous lots, based on the previous clinical studies and foreign clinical experience, disulfide bond variants are unlikely to affect the safety and efficacy of eculizumab. However, as the possibility that differences in disulfide bond heterogeneity affect the safety and efficacy of eculizumab can not be ruled out, a quantitative assay for determining the relative abundance of disulfide bond variants will be developed and the acceptance criteria will be established.

PMDA accepted the applicant's response that although no specification for disulfide bond variants is set

at present, an assay will be developed to control disulfide bond variants, taking account of previous clinical experience and the clinical need for eculizumab.

(1).2) Control of immunogenic glycans

Since eculizumab contains fucosylated biantennary *N*-linked oligosaccharides bearing immunogenic Neu5Gc or αGal (including Galα1-3Gal), PMDA asked the applicant to explain the influences of glycan structure and its heterogeneity on the safety of eculizumab and the need to include the Neu5Gc content in the specification and provide a justification for the specification limit for the αGal content.

The applicant responded as follows:

Glycans in the Fc region are considered to be inside eculizumab and not to be recognized by molecules in the body. No adverse events of anaphylactic shock etc. following the administration of eculizumab have been reported so far. The number of patients who developed HAHA was limited (see Review Report (1) "4.(iii).B.(5).7) Immunogenicity and human anti-human antibodies (HAHA)"). Therefore, these glycans are unlikely to affect the immunogenicity of eculizumab.

The glycan structure of eculizumab and its heterogeneity can be controlled by the drug substance specifications for glycan profile and the upper limit for the αGal content and there is no plan to include the Neu5Gc content in the specification at present. However, if adverse events considered associated with glycans are reported in the safety information in future, the acceptance criteria for glycans will be reviewed. The current specification limit for the αGal content was established based on the results of lot analyses (10 drug substance lots produced by July 2005) that were available at the time of setting the specification in the US/Europe (July 2008). Whether the specification limit should be reviewed will be determined, based on the analytical results on recently manufactured lots.

PMDA concluded that although the immunogenicity of Neu5Gc and Galα1-3Gal has not completely been defined at present, based on previous clinical experience, glycan structure is unlikely to affect the safety of eculizumab as long as glycosylation is controlled by the current specifications, and accepted the response. However, depending on future safety information, it is necessary to consider reviewing the acceptance criteria for glycans, etc.

(1).3) C5 binding assay

PMDA asked the applicant to provide a justification for the specification limits, taking account of the potencies of the clinical formulation and the proposed commercial formulation analyzed by the new assay employed in [redacted] 20[redacted] and clinical experience.

The applicant responded as follows:

The potencies of [redacted] lots of the proposed commercial formulation analyzed by the new assay were

871,237 to 1,149,500 BU/mg, which were within the current specification limits (700,000-1,300,000 BU/mg) and no new adverse events associated with a switch to the proposed commercial formulation analyzed by the new assay have been reported so far. Therefore, the performance of the new assay is considered to be comparable to that of the old assay and the same specification limits can be used. As analytical results are limited at present, whether the specification limits should be reviewed will be determined, based on future manufacturing experience.

PMDA accepted the response.

(1).4) Drug product specification

The applicant explained as follows:

Though IEF and hemolytic assay are included in the drug product specification in the US and Europe, IEF and hemolytic assay are not included in the drug product specification in Japan because it is difficult to perform these tests in Japan for the following reasons:

- Skills and experience are required for performing the tests.
- It is difficult to maintain the precision and reproducibility of the tests with limited drug product lots imported to Japan and perform the tests consistently.
- It is uncertain if the reagents used in hemolytic assay (chicken erythrocytes, etc.) can be procured in Japan.

The quality of the drug product to be marketed in Japan can be assured by the results of IEF and hemolytic assay performed at the time of its release. The drug product after release testing is stored and shipped under adequate control and shipping validation and quality assessments of the drug product before and after shipment have demonstrated that the quality of the drug product is unaffected.

PMDA requested the applicant to take the following actions:

If IEF and hemolytic assay can not be included in the drug product specification in Japan, these tests that are performed overseas should be performed as in-process controls in the drug product manufacturing process, for the time being. Since IEF can separate differently charged species, it is preferable to include IEF in the specification. Thus, a system under which IEF can be performed should be established promptly and IEF should be included in the drug product specification. According to the results of validation of hemolytic assay presented in the application dossier, the assay results tend to be inherently variable. From this and other reasons, it is understood that it is technically difficult to perform hemolytic assay in Japan. However, since hemolytic assay can assess the ability and capacity of eculizumab to achieve a biological effect (a pharmacodynamic effect), including hemolytic assay in the drug product specification in Japan in future should be considered.

The applicant responded as follows:
For the time being, the both tests will be performed as in-process controls. A system under which IEF can be performed in Japan will be established promptly after approval and IEF will be included in the drug product specification. Furthermore, the possibility of performing hemolytic assay in Japan will continue to be reviewed.

PMDA accepted the response.

(1).5) Conformity of raw materials of animal origin to the Standard for Biological Ingredients
US-sourced BSA that does not conform to the Standard for Biological Ingredients is used as a medium component in the preparation and preservation of the MCB and WCB and for cell culture. PMDA asked the applicant to explain the risk assessment of BSA, the benefit of eculizumab, and the timing of switching. The Standard for Biological Ingredients does not apply to US-sourced BSA that is used in the preparation and preservation of the MCB and WCB in accordance with "Partial Revision of the Standard for Biological Ingredients" (PFSB Notification No. 0705001 dated July 5, 2004).

The applicant responded as follows:
With respect to the risk of transmissible spongiform encephalopathy (TSE) infection associated with the use of this raw material, "geographical risk and risk of the specific parts used for raw materials of drugs etc." and "risks associated with treatment in the product manufacturing process and product usage" ("Handling of Risk Assessment etc. in Partial Change Applications for Drugs, Medical Devices, etc., Using Bovine Derived Raw Materials etc." [PFSB/ELD Notification No. 0801001 and PFSB/SD Notification No. 0801001 dated August 1, 2003]) were assessed. As a result, the total risk assessment score was "less than -3," which met a threshold to provide a certain safety assurance and the risk of TSE infection associated with the use of eculizumab is very low. At present, there is no effective existing therapy for the hemolysis of PNH and the medical benefit of eculizumab is high. Switching to New Zealand-sourced BSA is currently under consideration and a partial change application for switching to BSA sourced from another country will be filed by the 4th quarter of 2011.

PMDA considers as follows:
Although the risk of TSE infection associated with the use of eculizumab can not be excluded, the result of risk assessment indicates that its risk is very low. There is no effective therapy for the hemolysis of PNH at present and as eculizumab stabilized Hb levels and reduced transfusion requirements by reducing hemolysis in the TRIUMPH study, eculizumab is expected to become an effective therapy for the hemolysis of PNH (However, it is necessary to select patients carefully in view of safety concerns [e.g. theoretical increase in the risk of infection with *Neisseria meningitidis* etc.]). Therefore, the medical usefulness of eculizumab should outweigh the risks associated with the use of this raw material.

Based on the above, as this case falls under 4-1-(5) of the Standard for Biological Ingredients, there is no need to withhold the approval of eculizumab until the raw material is switched to that sourced from countries where no bovine spongiform encephalopathy (BSE) has been reported. However, it should be stated in the package insert that the risk of TSE infection can not be excluded and patients should be fully explained about this risk prior to the use of eculizumab.

The above conclusion is based on the premise that the product will be manufactured using the raw material that conforms to the Standard for Biological Ingredients as soon as it becomes possible.

(2) Results from clinical pharmacology studies

PMDA reviewed the applicant's response to the question as follows and considered that there are no major differences in the effect of eculizumab between Japan and overseas.

(2).1) Hemolytic activity over time in clinical studies

The measured hemolytic activity over time in the C02-001, TRIUMPH, SHEPHERD, and C07-001 studies are shown in Figure 4. There were no major differences in the results.

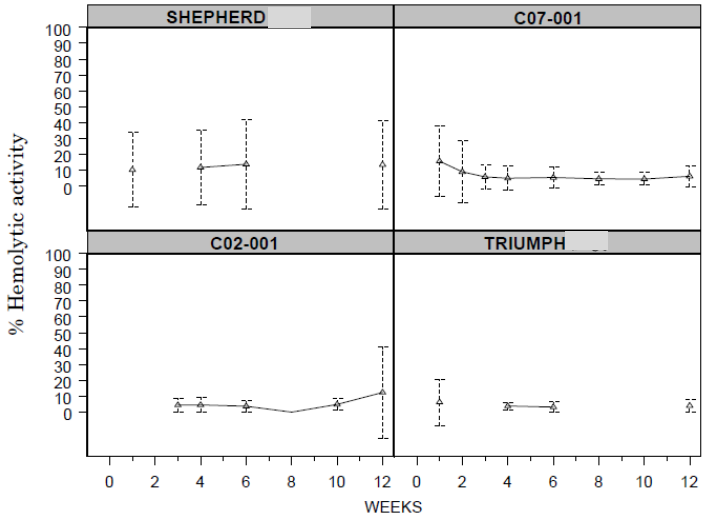


Figure 4. Hemolytic activity over time in clinical studies (C02-001, TRIUMPH, SHEPHERD, C07-001)

(3) Data subject to evaluation

For the review of the application, PMDA decided to position the foreign TRIUMPH study as the pivotal study and use the foreign SHEPHERD study and the Japanese C07-001 study as supporting efficacy and safety data, taking fully into consideration epidemiological differences in PNH between Japan and overseas and differences in patient background etc. among the studies, for evaluations, for the following reasons: since PNH is a rare disease, it is difficult to conduct a confirmatory clinical study in Japan alone; and since PNH is an acquired genetic disorder and eculizumab is an anti-C5 antibody, it is

inferred from the pathology of the disease and the mechanism of action that eculizumab is insensitive to ethnic factors.

The expert advisors made the following comment and supported the PMDA's decision:

- While TE is a clinical problem for PNH patients in the US and Europe, fewer patients develop TE and hematopoietic failure and renal impairment are more likely to become problems in Japan, etc., indicating differences in the clinical symptoms and causes of death of PNH between Japan and overseas. Therefore, what clinical significance is ultimately expected of hemolysis inhibition by eculizumab may be different between Japan and the US/Europe. However, as long as the efficacy of eculizumab is evaluated based on hemolysis inhibition, it is inferred that eculizumab is insensitive to ethnic factors.

(4) Efficacy

The following conclusions by PMDA were supported by the expert advisors:

Choosing "Hb stabilization" and "the number of PRBC units transfused" as the primary efficacy endpoints for the TRIUMPH study was appropriate for demonstrating the clinical significance of eculizumab as PNH patients primarily present with progressive anemia due to chronic intravascular hemolysis. Although the effects of eculizumab on the development of TE and survival prognosis etc. are undefined at present, as eculizumab was shown to be effective in maintaining Hb at levels that did not necessitate transfusions and reducing transfusion requirements in the TRIUMPH study, the clinical significance of hemolysis inhibition by eculizumab was demonstrated. The SHEPHERD study and Study C07-001 demonstrated reduction in hemolysis as indicated by changes of LDH, but have not assessed treatment effect, e.g. Hb stabilization.

PMDA reviewed the applicant's responses to the questions about efficacy as follows and considered that the efficacy of eculizumab can be expected.

(4).1) Influence of body weight

The applicant responded that there was no particular trend for the influence of body weight on the efficacy and safety of eculizumab in the TRIUMPH study, SHEPHERD study, and Study C07-001 and PMDA accepted the response.

(4).2) Long-term efficacy

LDH levels over time and transfusion requirements over time based on pooled analyses of the submitted foreign clinical studies (TRIUMPH, SHEPHERD, C02-001, E02-001, X03-001, X03-001A, E05-001) are shown in Tables 39 and 40, respectively. PMDA considered that it was suggested that continued treatment with eculizumab resulted in sustained decrease in hemolysis up to 24 months after start of treatment.

Table 39. LDH levels over time in foreign clinical studies[a)]

	Baseline	3 months	6 months	9 months	12 months	15 months	18 months	24 months
N	151	150	147	107	102	11	11	11
LDH (U/L)	2238.0 [511.8, 8600.0]	364.8 [126.7, 2594.0]	290.7 [111.7, 5117.0]	299.7 [109.3, 1192.3]	285.4 [103.0, 821.0]	528.5 [155.5, 755.0]	500.5 [157.5, 683.0]	532.0 [141.0, 740.0]

Median [Min., Max.]

a) TRIUMPH, SHEPHERD, C02-001, E02-001, X03-001, X03-001A, E05-001

Table 40. Transfusion requirements over time in foreign clinical studies[a)]

	Baseline[b)]	0-3 months	3-6 months	6-9 months	9-12 months	12-15 months	15-18 months	21-24 months
N	151	150	147	107	102	11	11	11
No. of units transfused	3.3 [0.0, 16.5]	0.0 [0.0, 16.0]	0.0 [0.0, 14.0]	0.0 [0.0, 12.0]	0.0 [0.0, 16.0]	2.0 [0.0, 6.0]	0.0 [0.0, 3.0]	0.0 [0.0, 5.0]

Median [Min., Max.]

a) TRIUMPH, SHEPHERD, C02-001, E02-001, X03-001, X03-001A, E05-001

b) The number of units transfused in the past 1 year divided by 4

(4).3) Lack of efficacy

PMDA asked the applicant about the details of 14 cases of lack of efficacy reported from foreign post-marketing surveillance (Table 32).

The applicant explained as follows:

Among the 14 patients diagnosed with lack of efficacy, 4 patients continued treatment, 8 patients discontinued treatment, and 2 patients had unknown status regarding treatment continuation. The reasons for classifying patients as lack of efficacy included complications (worsening of AA or MDS, etc.), inadequate doses, a hemolytic crisis associated with a reduced dose of steroids, no reduction in transfusion requirements, and death due to sepsis. Changes in LDH levels were reported in 6 of the 14 patients and treatment with eculizumab resulted in reductions in LDH levels in all 6 patients.

PMDA considered as follows:

Concerning the information on the patients reported as lack of efficacy via foreign post-marketing surveillance, there were patients classified as lack of efficacy in the judgment of the attending physician despite the fact that LDH levels were reduced following treatment with eculizumab. In the Japanese clinical study (C07-001), 2 patients were classified as lack of efficacy as LDH levels were not reduced. Based on these findings, it is necessary to continue to collect information on patients classified as lack of efficacy also after the market launch and investigate the reasons for classifying patients as lack of efficacy and the causes for lack of efficacy.

(5) Safety

(5).1) Overall safety of eculizumab

PMDA concluded as follows:

The incidences of adverse events of headache, nasopharyngitis, back pain, and fatigue tended to be higher in the eculizumab group than in the placebo group in the TRIUMPH study[††††] and attention

†††† In response to the request from PMDA, the applicant discussed that the causes for higher incidences of nasopharyngitis, back pain, and fatigue in the eculizumab group than in the placebo group in the TRIUMPH study are unknown.

should be paid to the possible occurrence of headache, especially during the early phase of treatment. There were no serious adverse events unique to the eculizumab group or no adverse events unique to long-term treatment. Thus, adverse events associated with eculizumab are tolerable.

On the other hand, based on its mechanism of action, eculizumab may increase the risk of infections with encapsulated bacteria (especially, *Neisseria meningitidis*) that are cleared by terminal complement components and attention should be paid to infections, especially meningococcal infection [see "(5).2) Meningococcal infections"]. Furthermore, since there is a concern about the development of a serious hemolytic crisis after eculizumab discontinuation due to the accumulation of PNH type III RBCs in patients being treated with eculizumab, the information on the risks associated with discontinuation of eculizumab and the need for monitoring patients after eculizumab discontinuation should be provided appropriately to the medical practice.

The above conclusions by PMDA were largely supported by the expert advisors, but the following comments were raised from some expert advisors.

- Although the incidence of headache was higher in the eculizumab group, as headache occurs also as an initial symptom of meningococcal infection, it may become necessary to differentiate the causes of headache. How headache is managed overseas should be checked, an appropriate approach to headache should be considered, and information should be provided to the medical practice.
- Theoretically, the risk of infections with not only *Neisseria meningitidis*, but also other encapsulated bacteria, e.g. *Streptococcus pneumoniae* and *Haemophilus influenzae*, may be increased. The status of vaccination against *Streptococcus pneumoniae* and *Haemophilus influenzae* in foreign countries where eculizumab has been approved should be checked and then the incidence of infections among eculizumab-treated patients in Japanese and foreign marketing experience should continue to be investigated and necessary actions should be taken.
- Theoretically, the risk of a serious, acute hemolytic crisis is increased after eculizumab discontinuation and adequate caution should be provided. For the cases of treatment discontinuation, the information after discontinuation should be collected.

PMDA asked the applicant to explain how to differentiate a headache associated with eculizumab from a headache caused by *Neisseria meningitidis*.

The applicant explained as follows:
It is difficult to specifically differentiate a headache associated with eculizumab from a headache caused by meningococcal infection if there are no other symptoms. Meanwhile, differentiation is considered possible in most cases based on (a) the presence or absence of other symptoms of meningococcal infection (pyrexia, nausea/vomiting, neck or back stiffness, rash, mental confusion, severe myalgia

accompanied by flu-like symptoms, photophobia) or (b) antipyretic analgesics are ineffective against a headache caused by meningococcal infection. Performing head tapping test, jolt accentuation test, vascular compression test, nerve compression test, muscle compression test, and tension sign tests etc. as appropriate and determining the presence or absence of symptoms of meningeal irritation due to bacterial meningitis should also be considered in order to diagnose the cause of headache.

However, basically, at the discretion of specialists, tests for infections (blood culture and lumbar puncture etc.) will be performed and antibiotics will be administered.

PMDA asked the applicant to explain the status of vaccination against *Streptococcus pneumoniae* and *Haemophilus influenzae* in foreign countries where eculizumab has been approved.

The applicant explained as follows:
The status of vaccination in a Japanese clinical study (C07-001) and foreign clinical studies (TRIUMPH, SHEPHERD) is shown in Table 41.

According to the foreign post-marketing data as of January 31, 2010 (1700 case reports), about 1% of patients were vaccinated against *Streptococcus pneumoniae* or *Haemophilus influenzae*, or both.

Table 41. Status of vaccination against *Streptococcus pneumoniae* and *Haemophilus influenzae* in Japanese and foreign clinical studies (TRIUMPH, SHEPHERD, C07-001)

Clinical study		No. of patients	No. of vaccinated patients	
			Streptococcus pneumoniae	*Haemophilus influenzae*
TRIUMPH	Eculizumab	43	0	2
	Placebo	44	0	2
SHEPHERD		97	2	22
C07-001		29	0	0

PMDA considers as follows:
Headache is an adverse event with a high incidence as the incidence of headache in patients treated with eculizumab was 51.3% (100 of 195 patients) in foreign clinical studies (TRIUMPH, SHEPHERD, C02-001, E02-001, X03-001, X03-001A, E05-001) and 58.6% (17 of 29 patients) in the Japanese clinical study (C07-001). Differentiating a headache as an adverse drug reaction from a headache caused by meningococcal infection is important and patients must understand that they should contact their doctors immediately if headache occurs during treatment with eculizumab. Adequate information on differentiation of headaches should be provided to patients and healthcare professionals.

Taking account of the overseas situation, there seems no need to mandate vaccination against *Streptococcus pneumoniae* and *Haemophilus influenzae* at present. However, as treatment with eculizumab may theoretically increase the risk of infections with *Streptococcus pneumoniae* and *Haemophilus influenzae*, physicians should be alerted to these infections and vaccination against *Streptococcus pneumoniae* and *Haemophilus influenzae* should be considered as appropriate, at the

discretion of the physician.

Based on the above discussion, PMDA instructed the applicant to appropriately provide information and issue an alert, based on the comments from the expert advisors, via the package insert and information leaflet. The applicant responded appropriately and PMDA accepted it.

(5).2) Meningococcal infections

PMDA concluded as follows:

Based on its pharmacological action, eculizumab may increase the risk of developing a meningococcal infection. As part of measures against meningococcal infections, patients are required to be immunized with a meningococcal vaccine prior to the use of eculizumab in the US/Europe (eculizumab is contraindicated in unvaccinated patients) and patients were required to be immunized with a meningococcal vaccine also in the TRIUMPH study, SHEPHERD study, and a Japanese clinical study (C07-001). Meningococcal vaccination can be used as a promising safety measure also in Japan. However, there is currently no approved meningococcal vaccine whose efficacy and safety have been demonstrated in Japanese subjects and the major tetravalent vaccines (serogroups A, C, Y, and W135), which are currently used overseas, are expected to have limited efficacy against serogroup B disease, which has been relatively commonly reported in Japan, etc. Thus, it is necessary to continue to review the need for meningococcal vaccination while collecting information actively from Japan and overseas. In order to reduce the risks associated with meningococcal infections, adequate measures against meningococcal infections, e.g. early detection and early initiation of treatment with antibiotics, should be taken. Adequate information on the risks and benefits of eculizumab should be provided to healthcare professionals and patients and eculizumab should be initiated after both the healthcare professional and patient understand the risks and benefits of eculizumab.

The expert advisors made the following comments on the above conclusions by PMDA:

- PNH patients with decreased white blood cells due to AA or MDS are susceptible to infections and especially among Japanese PNH patients, the proportion of patients with AA or MDS is relatively high. Therefore, if they develop a meningococcal infection, the disease is likely to become serious.
- Even if the major tetravalent meningococcal vaccines, which are currently used overseas, have limited efficacy in Japan, these vaccines can be expected to be effective in some patients. Therefore, at least, an environment where meningococcal vaccination is available upon request should be created.
- The regulatory authorities should guide the industry to proceed with the development of meningococcal vaccine in Japan.
- Since meningococcal infections will be manageable in most cases with early detection and appropriate early treatment, adequate information on infections, e.g. treatment with antibiotics,

should be provided and cooperation with a medical institution prepared to treat infections is needed.

- Prior to the use of eculizumab, adequate information on the risk of meningococcal infections should be provided to healthcare professionals. Patients should also be fully informed of the risk and their consent should be obtained before the initiation of treatment.

Taking account of the comments from the expert advisors, PMDA asked for the applicant's view on the provision of information on meningococcal infections and meningococcal vaccination after marketing approval of eculizumab.

The applicant explained meningococcal vaccination prior to the use of eculizumab as follows:
(a) In cooperation with a foreign vaccine manufacturer ([redacted]), a clinical trial of a tetravalent meningococcal vaccine (serogroups, A, C, Y, and W135) (brand name, [redacted]) intended for the prevention of meningococcal infections in PNH patients will be initiated as soon as possible in Japan.
(b) The following procedures will be followed until meningococcal vaccine receives marketing approval in Japan.

i) The physician identifies a PNH patient considered to require treatment with eculizumab and provides the patient with the information on the risk of developing a meningococcal infection associated with eculizumab, the prevention and treatment methods of meningococcal infections, and its efficacy and safety.
ii) Ask the patient if he/she wishes to receive meningococcal vaccine.
iii) If the patient wishes to receive meningococcal vaccine, ask the patient if he/she wishes to participate in a clinical trial of meningococcal vaccine. If the patient wishes not to participate in the clinical trial of meningococcal vaccine or the medical institution treating the patient does not participate in the clinical trial of meningococcal vaccine, provide the information on the private import method or the health facilities providing meningococcal immunization services for overseas travelers, etc.[‡‡‡‡] to the medical institution to explain to the patient.
iv) Deliver eculizumab after confirming that the patient has received meningococcal vaccine.
v) If the patient wishes not to receive meningococcal vaccine, receive a written pledge from the patient stating that the patient fully understands the risk of meningococcal infections and starts treatment with eculizumab, before delivery of eculizumab.

PMDA considers as follows:
In light of the current situation where there is no approved meningococcal vaccine in Japan, it is unavoidable at present to follow the procedures proposed by the applicant.

Since even meningococcal vaccination can not completely protect against meningococcal infections, as

‡‡‡‡ In cooperation with the Japanese Society of Travel and Health.

feasible measures to reduce the risks associated with meningococcal infections in Japan, measures against meningococcal infections, e.g. cooperation with a medical institution prepared to treat infections, early detection, and early initiation of treatment with antibiotics, should be built, adequate information on the risks and benefits of eculizumab should be provided to healthcare professionals and patients, and eculizumab should be initiated after both the healthcare professional and patient understand the risks and benefits of eculizumab.

The applicant responded that they will address accordingly and PMDA accepted it.

PMDA instructed the applicant to prepare the details of information leaflets before the market launch and the applicant responded that they will do so.

(5).3) Results of foreign post-marketing surveillance

In response to the request from PMDA, the applicant explained differences in observed adverse events between clinical studies and post-marketing surveillance as follows:

Hb decreased was observed in the foreign post-marketing surveillance only. This is possibly because PNH-related laboratory findings may have been regarded as adverse events in the post-marketing surveillance but were not reported as adverse events in the clinical studies. Thus, the differences in observed serious adverse events are considered to have no clinically relevant significance.

PMDA considers as follows:

Although no particular events were reported at a markedly higher incidence in the foreign post-marketing surveillance than in the clinical studies, it is necessary to continue to collect information on the cases of lack of efficacy, e.g. Hb decreased, via post-marketing surveillance etc. and provide the information to the clinical practice as appropriate.

(5).4) Adverse events in pooled Japanese and foreign clinical studies

In response to the request from PMDA, the applicant presented adverse events occurring in ≥ 10.0% of patients in either group during the entire treatment period in all clinical studies as shown in Table 42 and serious adverse events occurring in at least 2 patients in either group during the entire treatment period as shown in Table 43.

PMDA confirmed the following:

Even when adverse events occurring up to Week 12 in the TRIUMPH study, SHEPHERD study, and Study C07-001 and foreign clinical studies (TRIUMPH, SHEPHERD, C02-001, E02-001, X03-001, E05-001) were pooled with other clinical studies, there were no significant major differences compared with Tables 29 and 30 and no problematic adverse events or serious adverse events were reported in Japan compared with overseas.

Table 42. Adverse events occurring in ≥ 10.0% of patients in either group during the entire treatment period in clinical studies (Pooled analysis)

	Foreign clinical studies				Japanese clinical studies			Foreign clinical studies				Japanese clinical studies	
	Placebo (N = 44)		Eculizumab (N = 195)		Eculizumab (N = 29)			Placebo (N = 44)		Eculizumab (N = 195)		Eculizumab (N = 29)	
	Incidence	N	Incidence	N	Incidence	N		Incidence	N	Incidence	N	Incidence	N
Overall	90.9%	40	99.0%	193	100.0%	29	Arthralgia	9.1%	4	15.9%	31	3.4%	1
Headache	27.3%	12	51.3%	100	58.6%	17	Cough	9.1%	4	15.9%	31	3.4%	1
Nasopharyngitis	18.2%	8	42.1%	82	58.6%	17	Dizziness	11.4%	5	15.4%	30	3.4%	1
Nausea	11.4%	5	25.1%	49	20.7%	6	Pain in extremity	2.3%	1	14.4%	28	3.4%	1
Diarrhoea	11.4%	5	22.1%	43	17.2%	5	Influenza like illness	2.3%	1	11.3%	22	3.4%	1
Pyrexia	4.5%	2	16.9%	33	13.8%	4	Myalgia	2.3%	1	10.8%	21	3.4%	1
Anaemia	2.3%	1	3.6%	7	13.8%	4	Pharyngolaryngeal pain	9.1%	4	14.4%	28	0.0%	0
Conjunctival haemorrhage	0.0%	0	1.0%	2	13.8%	4	Abdominal pain	11.4%	5	12.8%	25	0.0%	0
Oedema	0.0%	0	0.0%	0	13.8%	4	Insomnia	6.8%	3	11.8%	23	0.0%	0
Upper respiratory inflammation	0.0%	0	0.0%	0	13.8%	4	Constipation	4.5%	2	11.8%	23	0.0%	0
Vomiting	11.4%	5	16.4%	32	10.3%	3	Viral infection	11.4%	5	11.3%	22	0.0%	0
Upper respiratory tract infection	22.7%	10	30.8%	60	6.9%	2	Urinary tract infection	9.1%	4	11.3%	22	0.0%	0
Back pain	9.1%	4	20.0%	39	3.4%	1	Contusion	6.8%	3	11.3%	22	0.0%	0

Japanese clinical studies (study duration, up to 38 weeks): C07-001 and E07-001 (Interim report)
Foreign clinical studies (study duration, up to 206 weeks): TRIUMPH, SHEPHERD, C02-001, E02-001, X03-001, X03-001A, and E05-001 (Interim report)

Table 43. Serious adverse events occurring in at least 2 patients in either group during the entire treatment period in clinical studies (Pooled analysis)

	Foreign clinical studies				Japanese clinical studies			Foreign clinical studies				Japanese clinical studies	
	Placebo (N = 44)		Eculizumab (N = 195)		Eculizumab (N = 29)			Placebo (N = 44)		Eculizumab (N = 195)		Eculizumab (N = 29)	
	Incidence	N	Incidence	N	Incidence	N		Incidence	N	Incidence	N	Incidence	N
Overall	20.5%	9	25.6%	50	13.8%	4	Headache	0.0%	0	2.1%	4	0.0%	0
Abdominal pain	0.0%	0	1.0%	2	0.0%	0	Convulsion	0.0%	0	1.0%	2	0.0%	0
Pyrexia	2.3%	1	3.6%	7	3.4%	1	Acute renal failure	0.0%	0	1.0%	2	3.4%	1
Cholelithiasis	0.0%	0	1.0%	2	0.0%	0	Nephrolithiasis	0.0%	0	1.0%	2	0.0%	0
Cellulitis	2.3%	1	1.0%	2	3.4%	1	PNH	6.8%	3	1.0%	2	0.0%	0
Viral infection	2.3%	1	2.6%	5	0.0%	0	Anaemia	2.3%	1	2.1%	4	3.4%	1
Viral gastroenteritis	0.0%	0	1.0%	2	0.0%	0	Haemolytic anaemia	0.0%	0	1.0%	2	0.0%	0
Septic shock	0.0%	0	1.0%	2	0.0%	0	Thrombocytopenia	0.0%	0	1.0%	2	0.0%	0
Intervertebral disc protrusion	0.0%	0	1.5%	3	0.0%	0	Neutropenia	4.5%	2	0.5%	1	0.0%	0

Japanese clinical studies (study duration, up to 38 weeks): C07-001 and E07-001 (Interim report)
Foreign clinical studies (study duration, up to 206 weeks): TRIUMPH, SHEPHERD, C02-001, E02-001, X03-001, X03-001A, and E05-001 (Interim report)

(6) Indication

PMDA concluded as follows:

Eculizumab is palliative and is not a curative therapy for PNH. Improvement in survival prognosis has not been demonstrated at present. Eculizumab may increase the risk of developing an infection with encapsulated bacteria, e.g. *Neisseria meningitidis*. Once treatment is initiated, continued treatment is needed. Taking account of these points, eculizumab should be used only in appropriate patients, fully examining treatment effects and potential risks. Therefore, the package insert should state that Hb stabilization and reductions in transfusion requirements have been demonstrated only in the TRIUMPH study population and advise that eculizumab should be used only if the clinical benefits are considered to outweigh the potential risks. It is also necessary to state that the efficacy of eculizumab during an acute hemolytic crisis has not been demonstrated.

The expert advisors made the following comments and supported the above conclusions by PMDA.

- PNH is considered associated with a relatively good survival prognosis, in view of the age of onset and survival time after diagnosis (Table 19). As the effects of eculizumab on the development of TE and survival prognosis are undefined, the significance of administering eculizumab to less transfusion-dependent patients is not high and it should be advised that eculizumab should be used in patients who are expected to require regular transfusions.
- Eculizumab reduces hemolysis, but may increase the risk of a serious hemolytic crisis due to the accumulation of PNH type III RBCs.
- Prior to the use of eculizumab, risk-benefit assessment is needed on an individual basis and it is difficult to define the intended population, but appropriate patients may be selected based on the patient populations enrolled in clinical studies.
- Given the risks associated with eculizumab, adequate information should be provided to ensure that eculizumab will not be initiated easily in patients in less need of treatment with eculizumab.
- In clinical practice, it is envisaged that treatment initiation will be considered if a patient is hospitalized due to an acute hemolytic crisis, etc. Thus, it should be stated that the efficacy of eculizumab in such cases is unknown.

Based on the above comments from the expert advisors, PMDA instructed the applicant to modify the proposed indication and precautions of indication statements of the package insert. The applicant responded that the statements will be modified as follows and PMDA accepted it.

[Indication]

Reduction of hemolysis in patients with paroxysmal nocturnal hemoglobinuria

[Precautions for indication]

- Treatment with Soliris should be initiated in patients with a diagnosis of paroxysmal nocturnal hemoglobinuria established by flow cytometry etc.
- Treatment with Soliris should be initiated in patients considered to require RBC transfusions due to hemolysis and expected to require regular transfusions.
- Prevention of thromboembolism, improvement in renal function, or survival benefit of Soliris has not been demonstrated.
- The efficacy of Soliris during an acute hemolytic crisis has not been demonstrated.
- Due to the following potential risks, after fully understanding the efficacy and safety of Soliris, whether or not to use Soliris should be determined carefully and treatment with Soliris should be initiated in appropriate patients (see “Clinical Studies”).
  - ► An increased risk of infections with *Neisseria meningitidis* etc. (Soliris inhibits complement C5 and may increase a patient’s susceptibility to infections with encapsulated bacteria, e.g. *Neisseria meningitidis*.)

► Development of a serious hemolytic crisis after Soliris discontinuation (As PNH RBCs increase in patients being treated with Soliris, serious intravascular hemolysis may be induced if Soliris is discontinued.)

(7) Dosage and administration

PMDA concluded as follows:

Although the rationale for the proposed dosage and administration is not necessarily sufficient, the TRIUMPH study has confirmed the efficacy of eculizumab, Study C07-001 in Japanese PNH patients also has suggested reduction in hemolysis, and based on the submitted clinical study data, eculizumab increases the risk of developing a meningococcal infection, but otherwise the safety profile of eculizumab is tolerable. Therefore, eculizumab has certain usefulness at the dosage regimen used in clinical studies in PNH patients. It should be stated in the precautions for dosage and administration section of the package insert that as a hemolytic crisis due to decreased blood concentrations may occur, the labeled dosage and administration instructions should be complied with and that if LDH levels are not reduced for a certain period of time, whether or not to continue treatment should be determined.

The above conclusions by PMDA were supported by the expert advisors and PMDA instructed the applicant to modify the dosage and administration and precautions for dosage and administration statements of the package insert.

The applicant explained that although LDH levels were reduced by Week 1 in the majority of patients, as it took about 2 weeks for LDH levels to be reduced in some patients, whether or not to continue treatment with eculizumab should be determined at around Week 2. The applicant then modified the dosage and administration and precautions for dosage and administration statements as follows and PMDA accepted it.

[Dosage and administration]

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.

[Precautions for dosage and administration]

- Diluted Soliris should be administered by intravenous infusion over 25 to 45 minutes via a dedicated infusion line.
- Comply with the recommended dosing intervals as an acute hemolytic crisis due to decreased blood concentrations of Soliris may occur.
- If serum lactate dehydrogenase (LDH) activity is not reduced by Week 2, whether or not to continue treatment with Soliris should be determined.

(8) Pediatric indication

In response to the questions on a pediatric indication, the applicant explained as follows:

Among 34 pediatric patients treated with eculizumab in the foreign marketing experience (as of August 24, 2009), 6 patients experienced serious adverse events ("central line infection" in 1 patient, "anaemia and *Pseudomonas aeruginosa* infection" in 1 patient, "tooth infection" in 1 patient, "thrombosis, abdominal pain, and constipation" in 1 patient, "bronchospasm" in 1 patient, "respiratory failure, cerebral aspergillosis, and enterococcal sepsis" in 1 patient). A causal relationship to eculizumab could not be denied for "anaemia and *Pseudomonas aeruginosa* infection" and no causality assessment was reported for "tooth infection," "thrombosis, abdominal pain, and constipation," and "bronchospasm."

Although there is no plan to develop eculizumab for Japanese pediatric patients with PNH at present, the development of eculizumab for pediatric use will be considered based on the planned foreign clinical study and the uses of eculizumab in Japan.

PMDA concluded as follows:

As it is known that children also develop PNH, a pediatric indication should also be considered. Due to very limited information on the efficacy and safety of eculizumab in children at present, for the time being, the phrase "adult dosage" should be included in the dosage and administration statement and it should be stated in the precautions section that "the efficacy and safety of eculizumab in children has not been established."

The following comment on the above conclusions by PMDA was raised from the expert advisors: as the risk of infections is different between adults and children, special caution is required when using eculizumab in children. The conclusions by PMDA were supported by the expert advisors.

If a pediatric patient treated with eculizumab is reported from a post-marketing surveillance study covering all treated patients, the case should be reviewed and it will be necessary to provide information and take safety measures as appropriate [see "(9) Post-marketing surveillance etc."].

(9) Post-marketing surveillance etc.

In response to the request from PMDA, the applicant explained an overview of the PNH registry, a foreign epidemiological study, as follows:

The objectives of the study are to capture the clinical courses of patients with PNH and to raise awareness of PNH among healthcare professionals and patients. In the study, patient demographics, the drugs used, disease progression, and clinical outcomes have been surveyed based on the data collected during patient visits.

The applicant explained that based on this PNH registry, a post-marketing survey (survey period, 8

years; a survey covering all treated patients) as shown in Table 38 will be conducted in Japan.

PMDA concluded that in addition to the items presented by the applicant, (a) PNH type III RBC clone over time (collect the information if analyzed), (b) the information on HAHA (antibody titers, neutralizing antibodies, etc.), and (c) the information on the use of eculizumab in children and pregnant women/nursing mothers should be collected. This conclusion was supported by the expert advisors. The expert advisors commented that the following items should also be included: (d) the reason for definitive diagnosis of PNH, (e) concurrent AA or MDS, (f) the information on the cases of lack of efficacy, (g) the information on the use of eculizumab during an acute hemolytic crisis, (h) the information on meningococcal infections (meningococcal carriage [if tested], a history of meningococcal infection, meningococcal vaccination status [vaccination date, vaccine type, etc.]), (i) detailed information on the development of infections including meningococcal infection, (j) the development of TE during treatment period, and (k) the reason for eculizumab discontinuation and the severity of hemolysis after discontinuation.

PMDA instructed the applicant to submit a draft outline of a post-marketing surveillance plan incorporating the above points and the applicant submitted an outline of a post-marketing surveillance plan (draft) as summarized in Table 44 and PMDA accepted it.

Table 44. Outline of post-marketing surveillance plan (draft)

Objectives	**・Detection of unknown and serious adverse drug reactions** **・Long-term safety and efficacy** **・Effects of eculizumab on the course of PNH (progression, course, and prognosis etc. of the disease)**
Survey period	**Re-examination period**
Planned number of patients	**All patients treated with eculizumab**
Target patient population	**Patients diagnosed with PNH**
Major items to be investigated	**(a) Patient background analysis:** **Indication for use: reduction of hemolysis in patients with paroxysmal nocturnal hemoglobinuria** **・The reason for definitive diagnosis of PNH (the basis of the diagnosis)** **Priority items (Patient background for safety)** **・Meningococcal carriage (if tested)** **Risk analysis of healthy carriers and noncarriers, Effects of eculizumab** **・History of meningococcal infection** **Risk analysis of patients with or without a history of meningococcal infection, Effects of eculizumab** **・Meningococcal vaccination (vaccination date, vaccine type)** **Risk analysis by vaccination status, vaccine type, and time after vaccination, Effects of eculizumab** **(b) Priority items (Safety)** **・Development of infections during treatment period (especially, *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*)** **Risk analysis of the development of infections, Effects of eculizumab** **・Development of thromboembolism during treatment period** **Risk analysis of the development of thromboembolism, Effectiveness of eculizumab** **・Presence or absence of concomitant medications for the prevention of thromboembolism** **Risk analysis of the development of thromboembolism, Effectiveness of concomitant medications** **・Development and severity of hemolysis after eculizumab discontinuation, the reason for discontinuation** **Safety analysis after the withdrawal of eculizumab** **・Development of headache** **symptoms (including associated symptoms), course, outcome, cause (meningococcal infection, other infections, infusion reactions to eculizumab, etc.), treatment instituted** **(c) Other items** **Information required for safety factor analysis will be focused, but efficacy items will also be investigated.** **・Concomitant medications:** **Effects of corticosteroids, immunosuppressants, erythropoietin, and anticoagulants on the safety and efficacy of eculizumab** **・Other medical history etc. (already cured/remitted before the initiation of treatment):** **Effects of eculizumab on the development (recurrence) of major vascular events and other diseases** **・Underlying disease (concurrent disease) etc.:** **Effects of AA, MDS, or other myeloid disorders on the safety and efficacy of eculizumab** **・PNH duration etc., Time after PNH diagnosis:** **Effects of time elapsed after definitive diagnosis on the effectiveness of eculizumab** **・Complications (comorbidities/symptoms) etc.:** **Effects of major vascular events, hepatic impairment/renal impairment, or the symptoms of other complications/comorbidities etc. on the safety and efficacy of eculizumab** **・Change in LDH from baseline over time** **・Improvement in QOL (fatigue, abdominal pain, dyspnoea, dysphagia)** **・Change in Hb from baseline over time** **・Change in the number of PRBC units transfused from baseline over time** **・Change from baseline in PNH type III or II RBCs (if analyzed)** **・Change from baseline in the percentage of PNH type I, II, or III RBCs as measured by flow cytometry (if analyzed)** **・Cases of lack of efficacy (Identify its cause)** **・Efficacy of eculizumab during an acute hemolytic crisis** **・Information on HAHA (antibody titers, neutralizing antibodies, etc.) (if assay is requested by the medical institution)**

III. Overall Evaluation

As a result of the above review, PMDA concludes that eculizumab may be approved after modifying the indication and dosage and administration statements as shown below, with the following conditions. As eculizumab is an orphan drug, the re-examination period is 10 years, the drug substance and the drug product are both classified as powerful drugs, and the product is classified as a biological product.

[Indication]
Reduction of hemolysis in patients with paroxysmal nocturnal hemoglobinuria

[Dosage and administration]
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.

[Conditions for approval]
1. Due to limited data from Japanese clinical studies, conduct a post-marketing drug use-results survey over a certain period of time, covering all patients treated with Soliris, in order to obtain the background information of patients treated with Soliris, collect data on the safety and efficacy of Soliris, and take necessary measures to ensure proper use of Soliris.
2. Prior to marketing Soliris, take necessary measures to ensure that Soliris will be administered only under the supervision of a physician at a medical institution, who is familiar with the diagnosis and treatment of paroxysmal nocturnal hemoglobinuria and is also fully capable of managing the risks etc. associated with Soliris in cooperation with a physician who is familiar with the diagnosis and treatment of meningococcal infection.