Report on the Deliberation Results

March 8, 2018

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

Brand Name	Hemlibra s.c. 30 mg
	Hemlibra s.c. 60 mg
	Hemlibra s.c. 90 mg
	Hemlibra s.c. 105 mg
	Hemlibra s.c. 150 mg
Non-proprietary Name	Emicizumab (Genetical Recombination) (JAN*)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	July 21, 2017

Results of Deliberation

In its meeting held on March 2, 2018, the Second 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 neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since only a limited number of Japanese patients have received the product, the applicant is required to conduct a drug use-results survey involving all Japanese patients treated with the product after the market launch until data from a certain number of patients have been gathered, in order to understand the characteristics of patients using the product, and to promptly collect safety and efficacy data so that necessary measures are taken to ensure proper use of the product.

**Japanese Accepted Name (modified INN)*

Review Report

February 13, 2018
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Hemlibra s.c. 30 mg Hemlibra s.c. 60 mg Hemlibra s.c. 90 mg Hemlibra s.c. 105 mg Hemlibra s.c. 150 mg
Non-proprietary name	Emicizumab (Genetical Recombination)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	July 21, 2017
Dosage Form/Strength	Injection: Each vial contains 30 mg, 60 mg, 90 mg, 105 mg, or 150 mg of Emicizumab (Genetical Recombination).
Application Classification	Prescription drug (1), Drug with a new active ingredient
Definition	Emicizumab is a recombinant bispecific humanized monoclonal antibody composed of complementarity-determining regions derived from rat anti-human blood coagulation factor IXa (FIXa) antibody and mouse anti-human blood coagulation factor X (FX) antibody, human framework regions and human IgG4 constant regions. In the anti-FIXa H-chain, the amino acid residues at position 202, 231, 299, 359, 412, 438 and 448 are substituted by Gln, Pro, Tyr, Lys, Lys, Arg and Pro, respectively, and Gly and Lys at the C-terminal are deleted. In the anti-FX H-chain, the amino acid residues at position 198, 227, 295, 408, 438 and 444 are substituted by Gln, Pro, Tyr, Lys, Glu and Pro, respectively, and Gly and Lys at the C-terminal are deleted. Emicizumab is produced in Chinese hamster ovary cells. Emicizumab is a glycoprotein (molecular weight: ca. 148,000) composed of an anti-FIXa H-chain (γ4-chain) consisting of 448 amino acid residues, an anti-FX H-chain (γ4-chain) consisting of 444 amino acid residues and 2 L-chains (κ-chains) consisting of 214 amino acid residues each.

Structure

Amino acid sequences and disulfide bonds:

L chain

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DIQMTQSPSS LSASVGDRVT ITCKASRNIE RQLAWYQQKP GQAPELLIYQ
ASRKESGVPD RFSGSRYGTD FTLTISSLQP EDIATYYCQQ YSDPPLTFGG
GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG
LSSPVTKSFN RGEC
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Anti-FIXa-H chain

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QVQLVESGGG LVQPGGSLRL SCAASGFTFS YYDIQWVRQA PGKGLEWVSS
ISPSGQSTYY RREVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARRT
GREYGGGWYF DYWGQGTLVT VSSASTKGPS VFPLAPCSRS TSESTAALGC
LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG
TQTYTCNVDH KPSNTKVDKR VESKYGPPCP PCPAPEFLGG PSVFLFPPKP
KDTLMISRTP EVTCVVVDVS QEDPEVQFNW YVDGVEVHNA KTKPREEQYN
STYRVVSVLT VLHQDWLNGK EYKCKVSNKG LPSSIEKTIS KAKGQPREPQ
VYTLPPSQKE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV
LDSDGSFFLY SKLTVDKSRW QEGNVFSCSV MHEALHNRYT QKSLSLSP
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Anti-FX-H chain

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QVQLVQSGSE LKKPGASVKV SCKASGYTFT DNNMDWVRQA PGQGLEWMGD
INTRSGGSIY NEEFQDRVIM TVDKSTDTAY MELSSLRSED TATYHCARRK
SYGYYLDEWG EGTLVTVSSA STKGPSVFPL APCSRSTSES TAALGCLVKD
YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY
TCNVDHKPSN TKVDKRVESK YGPPCPPCPA PEFLGGPSVF LFPPKPKDTL
MISRTPEVTC VVVDVSQEDP EVQFNWYVDG VEVHNAKTKP REEQYNSTYR
VVSVLTVLHQ DWLNGKEYKC KVSNKGLPSS IEKTISKAKG QPREPQVYTL
PPSQEEMTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTPPVLDSD
GSFFLYSKLT VDKSRWQEGN VFSCSVMHEA LHNHYTQESL SLSP
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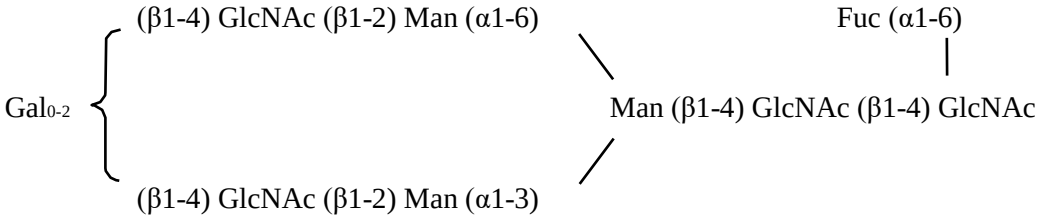
Partial pyroglutamic acid: Q1 in Anti-FIXa-H chain, Q1 in anti-FX-H chain

Glycosylation: N300 in Anti-FIXa-H chain, N296 in anti-FX-H chain

Disulfide bonds: C214 in L chain - C137 in anti-FIXa-H chain, C214 in L chain - C133 in anti-FX-H chain, C229 in anti-FIXa-H chain - C225 in anti-FX-H chain, C232 in anti-FIXa-H chain - C228 in anti-FX-H chain

Putative major carbohydrate structure



Molecular formula: $C_{6434}H_{9940}N_{1724}O_{2047}S_{45}$ (protein moiety, 4 chains)
Anti-FX-H chain: $C_{2164}H_{3334}N_{572}O_{690}S_{18}$
Anti-FIXa-H chain: $C_{2204}H_{3386}N_{588}O_{679}S_{15}$
L chain: $C_{1033}H_{1614}N_{282}O_{339}S_{6}$
Molecular weight: ca. 148,000

Items Warranting Special Mention

Orphan drug (Orphan Drug Designation No. 388 of 2016 [28 *yaku*], PSEHB/PED Notification No. 0824-7 dated August 24, 2016)

Reviewing Office Office of Vaccines and Blood Products

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in reducing bleeding tendency in patients with congenital blood coagulation factor VIII deficiency with blood coagulation factor VIII inhibitors, and that the product has acceptable safety in view of its benefits (see Attachment).

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

Indication

Reduction in bleeding tendency in patients with congenital blood coagulation factor VIII deficiency with blood coagulation factor VIII inhibitors

Dosage and Administration

The usual dosage is 3 mg/kg (body weight) of emicizumab (genetical recombination) subcutaneously administered once weekly for 4 doses, followed by 1.5 mg/kg (body weight) subcutaneously administered once weekly.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since only a limited number of Japanese patients have received the product, the applicant is required to conduct a drug use-results survey involving all Japanese patients treated with the product after the market launch until data from a certain number of patients have been gathered, in

order to understand the characteristics of patients using the product, and to promptly collect safety and efficacy data so that necessary measures are taken to ensure proper use of the product.

Attachment

Review Report (1)

January 10, 2018

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

Product Submitted for Approval

Brand Name	Hemlibra s.c. 30 mg Hemlibra s.c. 60 mg Hemlibra s.c. 90 mg Hemlibra s.c. 105 mg Hemlibra s.c. 150 mg (The proposed Japanese brand name was modified during the regulatory review, with no change to the English brand name)
Non-proprietary Name	Emicizumab (Genetical Recombination)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	July 21, 2017
Dosage Form/Strength	Injection: Each vial contains 30 mg, 60 mg, 90 mg, 105 mg, or 150 mg of Emicizumab (Genetical Recombination).

Proposed Indication

Reduction in bleeding tendency in patients with congenital blood coagulation factor VIII deficiency with blood coagulation factor VIII inhibitors

Proposed Dosage and Administration

The usual dosage is 3 mg/kg (body weight) of emicizumab (genetical recombination) subcutaneously administered once weekly for 4 doses, followed by 1.5 mg/kg (body weight) subcutaneously administered once weekly.

Table of Contents

List of Abbreviations

See Appendix.

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

Hemophilia A (congenital blood coagulation factor VIII deficiency) is a hemorrhagic disease caused by quantitative reduction or qualitative abnormality of blood coagulation factor VIII (FVIII) and may lead to serious bleeding episodes.

The primary therapy for patients with hemophilia A is to administer an adequate dose of FVIII product to ensure normal hemostasis. Some patients, however, may develop inhibitors (neutralizing antibodies) against administered FVIII that can significantly reduce the hemostatic effect of the FVIII product, rendering hemostasis difficult. Patients with hemophilia A with FVIII inhibitors, when experiencing acute bleeding or undergoing surgery, receive (a) a high-dose FVIII replacement therapy to neutralize the inhibitors in plasma and to increase the FVIII activity to a coagulable level and (b) a bypassing therapy to achieve hemostasis through a blood coagulation pathway not involving FVIII. In Japan, 3 bypassing products are approved: an activated prothrombin complex concentrate (aPCC) product (Feiba NF Intravenous), an activated blood coagulation factor VIIa concentrate containing factor X (FVIIa/FX) product (Byclot Combination Intravenous Injection), and a recombinant activated factor VII (rFVIIa) product (NovoSeven HI for Intravenous Injection).

Emicizumab (Genetical Recombination) (hereinafter referred to as emicizumab) is a humanized bispecific monoclonal antibody that binds to activated factor IX (FIXa) and factor X (FX). The resulting bridge between FIXa and FX serves as a cofactor in place of FVIII. Emicizumab is thus expected to reduce bleeding tendency in patients with hemophilia A with FVIII inhibitors.

For development of emicizumab, a global phase III clinical study in patients with hemophilia A with inhibitors (Study BH29884) was initiated in 14 countries including Japan in November 2015. Based on results from the study and other data, the applicant submitted a marketing application. In the US and Europe, marketing application for emicizumab was submitted in June 2017. Emicizumab was approved in the US in November 2017 and was under review in Europe as of December 2017.

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

2.1 Drug substance

2.1.1 Generation and control of cell substrate

Emicizumab is a bispecific humanized immunoglobulin G (IgG)4 antibody that has 2 complementarity-determining regions (CDRs) for FIXa and FX, its antigens. Genes of emicizumab code anti-FIXa H chain, anti-FX H chain, and κ-type L chain. The CDR sequence in the anti-FIXa H chain gene is derived from the H chain gene of a rat anti-human FIXa antibody, while that in the anti-FX H chain gene is derived from the H chain gene of a mouse anti-human FX antibody. To optimize properties of the bispecific antibody that has an anti-FIXa H chain and anti-FX H chain, amino acid substitutions were introduced in the variable region and constant region of each H chain through gene manipulation. The CDR sequence in the L chain gene is derived from gene sequence of a L chain that is compatible with both H chains to FIXa and FX and was selected using chimera antibodies with L chains from the rat anti-human FIXa antibody and mouse anti-human FX antibody in combination based on the binding affinity to both antigens (*PLoS ONE.* 2013;8:e57479). [redacted] prepared by

inserting gene fragments that code H chain and L chain [redacted] into [redacted].

From Chinese hamster ovary (CHO) cells transfected with [redacted], an optimum cell line for manufacture of emicizumab was isolated. This cell line was used to prepare a master cell bank (MCB) and a working cell bank (WCB).

The MCB, WCB, and cells at the limit of *in vitro* age (CAL) were characterized and subjected to purity tests in accordance with International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q5A (R1), Q5B, and Q5D. The results demonstrated genetic stability in the cell bank systems and during manufacturing. At least for items tested, neither adventitious viruses nor non-viral adventitious agents were detected except for endogenous retrovirus-like particles that are commonly seen in CHO cells.

The MCB and WCB are stored in a vapor phase of liquid nitrogen. [redacted], additional WCBs are generated as needed.

2.1.2 Manufacturing process

The manufacturing process of the drug substance consists of culture and harvest (passage culture, seed culture, production culture, harvest), purification ([redacted], [redacted] treatment [virus inactivation], [redacted], [redacted], [redacted], virus removal [redacted], [redacted] filtration, and adjustment/filtration/filling), and storage and testing. The obtained drug substance is stored in [redacted] at ≤[redacted]°C.

Critical steps are [redacted], [redacted], [redacted], [redacted], [redacted], [redacted] filtration, and [redacted] filtration.

The manufacturing process for the drug substance was subjected to a process validation on a commercial scale.

2.1.3 Safety evaluation of adventitious agents

No biological materials other than the CHO cells, host cells, are used in the manufacturing process of the drug substance. The CHO cells were confirmed to conform to the Standard for Biological Ingredients.

The MCB, WCB, and CAL were subjected to purity tests, and neither adventitious viruses nor non-viral adventitious agents were detected.

Pre-harvest unpurified bulk obtained at the commercial scale was subjected to tests for bioburden, mycoplasma, adventitious viruses (*in vitro*), and mouse minute virus (MMV) (*in vitro*) as well as transmission electron microscopy. At least for the items tested, neither adventitious viruses nor non-viral adventitious agents were detected except for endogenous retrovirus-like particles. In addition, the pre-harvest unpurified bulk is to be controlled by in-process control tests that cover mycoplasma, bioburden, adventitious viruses (*in vitro*), and MMV (*in vitro*).

A viral clearance study using model viruses was conducted for the purification process (Table 1). The result has shown that the purification has certain virus clearance capacity. The virus reduction factor for each process shown in the table below is the lowest value among those obtained from multiple independent test results (for the processes of [redacted] and [redacted], test results with recycled resin were included).

Table 1. Results from viral clearance study

Manufacturing process	Virus reduction factor (log10)		
	Murine leukemia virus	Minute virus of mice	Simian virus 40
[redacted]	[redacted]	[redacted]	[redacted]
[redacted] treatment	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Virus removal [redacted]	[redacted]	[redacted]	[redacted]
Overall virus reduction factor	≥18.93	≥12.00	≥13.90

2.1.4 Manufacturing process development

The following are major changes made to the manufacturing process during the development of the drug substance:

- Change of [redacted] and change of [redacted]
- Change of [redacted] and [redacted]
- Change of [redacted] (introduction of [redacted], change of [redacted], change of [redacted])
- Change of [redacted] (introduction of [redacted], change of the manufacturing process [redacted], [redacted], change of [redacted], introduction of [redacted], and change of [redacted] and [redacted])
- Change of [redacted] concentration

Phase I study used the product prepared from the drug substance manufactured in the pre-change manufacturing process (Process A), and phase III studies used the product prepared from the drug substance manufactured in the post-change manufacturing process (Process B, proposed process) [see Sections 7.1 and 7.3]. A bioavailability study used both products [see Section 6.1.1].

In association with these process changes, comparability in quality attributes between the pre-change and post-change drug substances was demonstrated.

The manufacturing process development employs Quality by Design (QbD) techniques [see Section 2.3].

2.1.5 Characterization

2.1.5.1 Structure and characterization

Characterization was performed as shown in Table 2.

Table 2. Summary of characterization

Item	
Structure	• Primary structure, disulfide bonds, free thiol groups • Amino acid modification (, , ,) • Carbohydrate structure ( ) • Higher order structure
Physicochemical properties	• Molecular weight • Isoelectric point • Molecular variants (, ,)
Biological properties	• (,) • Binding affinity to antigen ( ) ( ) • Binding affinity to (,)

2.1.5.2 Product-related substances/Product-related impurities

Based on characterization results and other data, the following product-related substances and product-related impurities were identified:

Product-related substances: Variant A-1 ( ), Variant B-1 ( ), Variant C, and Variant D-1 ( )

Product-related impurities: Variant E ( ), Variant F ( ), Variant A-2 , Variant B-2 ( ), Variant G, and Variant D-2 ( )

Of the product-related impurities, Variant E, Variant F, and Variant A-2-1 ([1)] and [2)]) are appropriately controlled by the specifications for the drug substance and/or drug product. The other product-related impurities have been demonstrated to be contained in the drug substance and/or drug product at a consistent level or to be adequately removed by the manufacturing process.

2.1.5.3 Process-related impurities

Host cell proteins, host cell DNA, , , and were identified as process-related impurities. All process-related impurities have been demonstrated to be adequately removed by the manufacturing process. Bacterial endotoxins and microbial limits are controlled by the specifications for the drug substance and drug product.

2.1.6 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (peptide map), pH, purity (and), bacterial endotoxins, microbial limit, , and assay (protein content and potency).

2.1.7 Stability of drug substance

Table 3 lists major stability studies for the drug substance.

1)
2)

Table 3. Summary of major stability studies for the drug substance

	Number of batches	Storage condition	Study period	Storage form
Long-term testing	5	[redacted] ± [redacted] °C	[redacted] months[a]	[redacted]
Accelerated testing	11	[redacted] ± [redacted] °C	[redacted] months	
Stress testing	4	[redacted] ± [redacted] °C, [redacted] % RH	[redacted] weeks	[redacted]

a Ongoing until [redacted] months

The long-term testing showed no clear changes in quality attributes throughout the study period, and the specimens conformed to the specifications.

The accelerated testing showed [redacted].

The stress testing showed [redacted].

Based on the above, a shelf life of 30 months has been proposed for the drug substance when stored in [redacted] at ≤ [redacted] °C.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is supplied as an injection, containing 30, 60, 90, 105 or 150 mg of the active ingredient per vial. The drug product contains excipients: L-histidine, L-aspartic acid, L-arginine, Poloxamer 188, and water for injection. The primary container consists of a glass vial (3-mL) and a butyl rubber stopper, and the secondary package is a paper carton.

2.2.2 Manufacturing process

The manufacturing process of the drug product consists of preparation of the drug solution (thawing, dilution, and filtration), sterile filtration, filling and stoppering, crimping, inspection, packaging and labeling, and storage and testing. Critical steps include [redacted].

The manufacturing process for the drug product was subjected to a process validation on a commercial scale.

2.2.3 Manufacturing process development

During the development of the drug product, [redacted] and [redacted] were changed, and [redacted]. Then, the comparability of quality attributes of drug products was demonstrated.

The drug product manufactured in the pre-change process was used in the phase I study [redacted] (Section 7.1 [redacted]).

The manufacturing process development employed QbD techniques [see Section 2.3].

2.2.4 Control of drug product

The proposed specifications for the drug product include content, description, identification (peptide map), osmolarity, pH, purity (size-exclusion chromatography [SEC], [redacted], and [redacted]), bacterial endotoxins, extractable volume, foreign insoluble matter, insoluble particulate matter, sterility, potency, and assay (protein content).

2.2.5 Stability of drug product

The 60-, 90-, 105-, and 150-mg drug products contain emicizumab at the same concentration in the same container and closure system, but differ only in volume (the 30-mg drug product uses a different emicizumab concentration). For the present application, the applicant conducted a stability testing with a bracketing design (the 60-and 150-mg drug products manufactured at commercial scale were used as samples on the extremes) and a stability study of the 30-mg drug product.

Table 4 shows major stability studies for the drug product.

Table 4. Summary of major stability studies for the drug product

	Number of batches		Storage condition	Study period	Storage form
	60 mg, 150 mg	30 mg			
Long-term testing	4 for each strength	3	5 ± 3°C	[redacted] months[a]	Glass vial with [redacted] rubber stopper
Accelerated testing	7 for each strength	6	[redacted] ± [redacted]°C, [redacted]% RH	[redacted] months	
Stress testing	3 for each strength	6	[redacted] ± [redacted]°C, [redacted]% RH	[redacted] weeks	
Photostability testing	1 (60 mg)	1	Overall illumination of ≥1.2 million lx·h An integrated near ultraviolet energy of ≥200 W·h/m^2		Glass vial with [redacted] rubber stopper (with or without a paper carton)

a Ongoing until [redacted] months

The long-term testing showed no clear changes in quality attributes throughout the study period, and the specimens conformed to the specifications.

The accelerated testing showed [redacted].

The stress testing showed [redacted].

The photostability testing showed a change in [redacted] and [redacted]. The drug product was photolabile.

Based on the above, a shelf life of 24 months has been proposed for the drug product when stored using glass vials protected from light at 2°C to 8°C.

2.3 QbD

In the development of the drug substance and drug product, QbD techniques have been used to formulate control strategy of their quality. Based on quality attributes of the drug substance and drug product including product-related substances, product-related impurities, and process-related impurities, the following critical quality attributes (CQAs) were identified. Process parameters, in-process control, and specifications have been established through process validation, consistency evaluation for each process,

and characterization of multiple batches, and thereby the quality attributes of the drug substance and drug product are controlled.

CQAs for the drug substance: [redacted], process-related impurities ([redacted]), adventitious agents, [redacted], and [redacted]

CQAs for the drug product: [redacted], insoluble particulate matter, foreign insoluble matter, [redacted], sterility, and [redacted]

2.R Outline of the review conducted by PMDA

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

2.R.1 Novel excipients

The drug product contains L-aspartic acid in an amount exceeding that contained in any existing products for subcutaneous injection.

2.R.1.1 Specifications and stability

Because L-aspartic acid conforms to the requirements in the Japanese Pharmacopoeia, PMDA has concluded that the specifications and stability are acceptable.

2.R.1.2 Safety

Based on the submitted data, PMDA has concluded that L-aspartic acid is unlikely to raise safety problems.

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

The applicant submitted data on primary pharmacodynamics of emicizumab: results from *in vitro* studies that investigated the pharmacological properties and *in vivo* studies in cynomolgus monkeys. The applicant also submitted results from *in vitro* secondary pharmacodynamics studies that investigated binding affinity to Fc receptor and complement C1q, safety pharmacology studies in cynomolgus monkeys, and pharmacodynamic drug interaction studies (*in vitro* study in human plasma and *in vivo* study in cynomolgus monkeys).

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies

The applicant submitted the following study data for evaluation of actions and properties of emicizumab, which serves as a cofactor in place of FVIII.

3.1.1.1 Binding affinity to FIX and FX (CTD 4.2.1.1.1, Study PHM[redacted]-0180; CTD 4.2.1.1.2, Study PHM[redacted]-0041S)

Binding affinity of emicizumab to human factor IX (FIX), FIXa, FX, and activated factor X (FXa) as well as cynomolgus monkey FIX and FX was investigated by surface plasmon resonance (SPR). All of the factors investigated bound to emicizumab. Natalizumab (anti-human α4 integrin antibody, negative control), which is an IgG4 antibody of the same subclass as emicizumab, did not bind to any of the factors. The study also showed concentration-dependent binding affinity of human FIX and human FIXa to variable regions of emicizumab that recognize FIX and FIXa, and concentration-dependent binding affinity of human FX and human FXa to variable regions of emicizumab that recognize FX and FXa.

3.1.1.2 Effect of emicizumab on FX activation (CTD 4.2.1.1.3, Study PHM[redacted]-0144; CTD 4.2.1.1.4, Study PHM[redacted]-0120)

Activation of human FX (formation of FXa) by emicizumab (0.01-1000 μg/mL) was measured with and without human FIXa at 0.05 μg/mL by a synthetic substrate method. Activation of FX was found to be dependent on concentration of emicizumab and presence of human FIXa. In addition, activation of FX by emicizumab (1-1000 μg/mL) was evaluated using cynomolgus monkey, rat, and mouse FIXa and FX molecules by a synthetic substrate method. Activation of FX was observed only with cynomolgus monkey FIXa and FX molecules.

3.1.1.3 APTT and thrombin formation study using FVIII deficient human plasma (CTD 4.2.1.1.5, Study PHM[redacted]-0139; CTD 4.2.1.1.6, Study PHM[redacted]-0143)

Emicizumab (0.0001-1000 μg/mL) was added to FVIII deficient human plasma to measure activated partial thromboplastin time (APTT). APTT tended to decrease with increase in the amount of emicizumab. Emicizumab (0.01-1000 μg/mL) was added to FVIII deficient human plasma to evaluate the amount of thrombin formed. Formation of thrombin was enhanced with increase in the amount of emicizumab.

3.1.1.4 Thrombin formation study using FVIII neutralizing plasma (CTD 4.2.1.1.7, Study PHM[redacted]-0204)

The amount of thrombin formed by emicizumab was evaluated using cynomolgus monkey and human plasma specimens in which FVIII was neutralized with anti-FVIII neutralizing antibody (10 specimens for each species). When recombinant porcine FVIII which was not neutralized by anti-FVIII neutralizing antibody but was active in both cynomolgus monkey and human plasma specimens was used as a standard, concentrations of emicizumab (geometric mean) equivalent to 0.01 and 0.05 U/mL of the standard were 4.81 and 67.1 μg/mL in cynomolgus monkey plasma and 2.52 and 27.0 μg/mL in human plasma. The amount of thrombin formed increased with increase in the amount of emicizumab.

3.1.2 *In vivo* study

The applicant submitted the following study data for the evaluation of the ability of emicizumab to reduce bleeding tendency and stop bleeding.

3.1.2.1 Effects of emicizumab in a puncture-induced bleeding model of FVIII-neutralized cynomolgus monkeys

Two studies (see the Sections below) were conducted using a bleeding cynomolgus monkey model (n = 4-6 males/group). The monkeys were given intravenous administration of anti-FVIII neutralizing antibody (10 mg/kg) to reduce the FVIII activity and, approximately 2 hours later, bleeding was induced by intramuscular puncture and subcutaneous detachment. In these studies, recombinant porcine FVIII was used as a control substance.

3.1.2.1.1 Effects of subcutaneous emicizumab (CTD 4.2.1.1.11, Study PHM[redacted]-0118; CTD 4.2.1.1.12, Study PHM[redacted]-0158; CTD 4.2.1.1.13, Study PHM[redacted]-0112)

Reduction in bleeding tendency by subcutaneous emicizumab was investigated in a puncture-induced bleeding model of FVIII-neutralized cynomolgus monkeys. Cynomolgus monkeys subcutaneously received a single dose of emicizumab at 0.3, 1, or 3 mg/kg 4 days before bleeding induction; intravenously received recombinant porcine FVIII (1 U/kg) twice daily from the day of bleeding induction (Day 0) to Day 2; or received nothing (negative control) after administration of anti-FVIII neutralizing antibody. On Day 3, blood hemoglobin level and bruising area were evaluated. The emicizumab and recombinant porcine FVIII groups showed higher blood hemoglobin levels and smaller bruising areas than the negative control group (Table 5).

Table 5. Reduction in bleeding tendency by subcutaneous emicizumab 0.3, 1, and 3 mg/kg (mean ± standard deviation [SD])

Group		N	Relative blood hemoglobin level[a]	Bruising area on the skin surface (cm^2)
Negative control (no treatment)		6	54 ± 22	208 ± 50
Subcutaneous emicizumab	0.3 mg/kg	4	64 ± 25	122 ± 66
	1 mg/kg	6	74 ± 11	84 ± 47
	3 mg/kg	6	80 ± 14	68 ± 51
Intravenous recombinant porcine FVIII		6	79 ± 14	77 ± 43

a Relative to the pre-bleeding level (100) in the negative control group

Similar results were obtained from a study in which a single dose of emicizumab at 10 or 50 mg/kg, or vehicle (negative control) was subcutaneously administered 4 days before bleeding induction (Table 6).

Table 6. Reduction in bleeding tendency by subcutaneous emicizumab 10 and 50 mg/kg (mean ± SD)

Group		N	Relative blood hemoglobin level[a]	Bruising area on the skin surface (cm^2)
Negative control (vehicle)		4	77 ± 2	157 ± 81
Subcutaneous emicizumab	10 mg/kg	4	90 ± 15	62 ± 85
	50 mg/kg	4	98 ± 5	18 ± 26

a Relative to the pre-bleeding level (100) in the negative control group

3.1.2.1.2 Effects of intravenous emicizumab (CTD 4.2.1.1.14, Study PHM[redacted]-5054)

Hemostatic effects of intravenous emicizumab were investigated in a puncture-induced bleeding model of FVIII-neutralized cynomolgus monkeys. Cynomolgus monkeys intravenously received emicizumab at 0.3, 1, or 3 mg/kg on the day of bleeding induction (Day 0); or intravenously received recombinant

porcine FVIII at 3.4 or 10 U/kg once on Day 0 and then twice daily on Days 1 and 2 (5 doses in total). On Day 3, blood hemoglobin level and bruising areas were evaluated. The emicizumab and recombinant porcine FVIII groups showed higher blood hemoglobin levels and smaller bruising areas than the negative control group (Table 7).

Table 7. Hemostatic effects of intravenous emicizumab 0.3, 1, and 3 mg/kg (mean ± SD)

Group		N	Relative blood hemoglobin level[a]	Bruising area on the skin surface (cm^2)
Negative control (no treatment)[b]		6	54 ± 22	208 ± 50
Emicizumab	0.3 mg/kg	4	61 ± 10	145 ± 50
	1 mg/kg	4	76 ± 23	75 ± 16
	3 mg/kg	4	82 ± 9	104 ± 49
Recombinant porcine FVIII	3.4 U/kg	4	67 ± 11	142 ± 79
	10 U/kg	4	84 ± 12	74 ± 83

a Relative to the pre-bleeding level (100) in the negative control group
b The negative control (no treatment) group in Table 5

3.1.2.2 Effects of subcutaneous emicizumab in a spontaneous bleeding model of FVIII-neutralized cynomolgus monkeys (CTD 4.2.1.1.15, Study PHM[redacted]-0049)

Cynomolgus monkeys (n = 1-4 males/group) whose FVIII activity was continuously suppressed by once-weekly intravenous doses of anti-FVIII neutralizing antibody, received emicizumab (initial dose 3.97 mg/kg, subsequent doses 1 mg/kg) or vehicle (negative control) subcutaneously once weekly for 8 weeks; or recombinant porcine FVIII (20 U/kg) intravenously twice weekly for 8 weeks. Bleeding tendency was evaluated based on the lowest blood hemoglobin level during the observation period, number of days without bleeding episode, number of days with claudication, and number of joints with intra-articular bleeding. The results showed that the bleeding tendency was suppressed in the emicizumab and recombinant porcine FVIII groups compared with the vehicle group (Table 8).

Table 8. Reduction in bleeding tendency by subcutaneous emicizumab (mean ± SD)

Group	N	Lowest blood hemoglobin level	Number of days without bleeding episodes	Number of days with claudication	Number of joints with intra-articular bleeding
Vehicle	4	75.2 ± 11.3	6.5 ± 6.8	25.0 ± 8.3	2.0 ± 0.8
Emicizumab	3	94.9 ± 4.9	33.3 ± 6.1	0.0 ± 0.0	0.0 ± 0.0
Recombinant porcine FVIII	1	94.9	28	0	2

3.1.2.3 Effects on thrombus formation in a venous congestion model of cynomolgus monkeys (CTD 4.2.1.1.19, Study PHM[redacted]-0008)

Following administration of emicizumab (1 or 2 mg/kg), activated factor VII (FVIIa) (120 μg/kg), or FVIII (25 U/kg) to cynomolgus monkeys, a vein was ligated to induce congestion (n = 4-5 males/group). In the negative control, a vein was ligated to induce congestion without any administration (n = 5 males/group). Thrombus formation was evaluated 1.5 hours after congestion. While thrombus was scarcely formed in the negative control group, thrombi were formed in the emicizumab, FVIIa, and FVIII groups.

3.2 Secondary pharmacodynamics

The applicant submitted the following study data for binding affinity of emicizumab to Fc receptor and complement C1q. The applicant considered that, based on the study results, the constant regions of emicizumab are unlikely to have an effector effect.

3.2.1 Binding affinity to human and cynomolgus monkey Fcγ receptors (CTD 4.2.1.2.1, Study PHM[redacted]-0177)

Binding affinity to human and cynomolgus monkey Fcγ receptors was investigated by SPR. Binding of emicizumab to these receptors did not clearly increase compared with that of IgG1 antibody rituximab (anti-human CD20 antibody) and IgG4 antibody natalizumab.

3.2.2 Binding affinity to human and cynomolgus monkey fetal Fc receptors (CTD 4.2.1.2.2, Study PHM[redacted]-0081)

Binding affinity to human and cynomolgus monkey fetal Fc receptors was investigated by SPR. Emicizumab showed pH-dependent binding affinity to these receptors as with IgG4 antibody natalizumab.

3.2.3 Binding affinity to human complement C1q (CTD 4.2.1.2.3, Study PHM[redacted]-0061)

Binding affinity to human complement C1 subunit C1q was investigated by enzyme-linked immunoassay (ELISA). Binding affinity of emicizumab and IgG4 antibody natalizumab was lower than that of IgG1 antibody rituximab.

3.3 Safety pharmacology

Effects of emicizumab on the central nervous system, cardiovascular system, and respiratory system are shown in Table 9. All of the effects were evaluated in repeated-dose toxicity studies [see Section 5.2].

Table 9. Summary of safety pharmacology studies

Organ system	Test system	Endpoint and method	Maximum dose	Route of administration	Findings	CTD
Central nervous system	Cynomolgus monkeys (n = 3-5/sex/ group)	Clinical signs, neuroethological function, pathological examination	30 mg/kg	Subcutaneous	No effects of emicizumab on the central nervous system	4.2.3.2.2
		Clinical signs, pathological examination	30 mg/kg	Subcutaneous		4.2.3.2.3
		Clinical signs, pathological examination	100 mg/kg	Intravenous		4.2.3.2.4
Cardiovascular system		Clinical signs, electrocardiogram, pathological examination	30 mg/kg	Subcutaneous	No effects of emicizumab on the cardiovascular system	4.2.3.2.2
			30 mg/kg	Subcutaneous		4.2.3.2.3
			100 mg/kg	Intravenous		4.2.3.2.4
Respiratory system		Clinical signs, pathological examination	30 mg/kg	Subcutaneous	No effects of emicizumab on the respiratory system	4.2.3.2.2
			30 mg/kg	Subcutaneous		4.2.3.2.3
			100 mg/kg	Intravenous		4.2.3.2.4

3.4 Pharmacodynamic drug interactions

The applicant submitted results of an *in vitro* study using human plasma and an *in vivo* study using cynomolgus monkeys (see the sections below). These studies evaluated the interactions of emicizumab

with FVIII, FVIIa, and aPCC, which are potentially coadministered with emicizumab in clinical practice. According to the applicant, *in vitro* coadiministration enhanced thrombin formation through the interaction, but *in vivo* coadiministration did not clearly increase the risk of thrombus formation.

3.4.1 Effects on thrombin formation in hemophilia A human plasma (CTD 4.2.1.1.8, Study PHM[redacted]-0198)

Effects of emicizumab on thrombin formation induced by FVIII (octocog alfa), FVIIa, and aPCC were investigated using hemophilia A human plasma *in vitro*. Thrombin formation was enhance by the interaction between emicizumab and each agent.

3.4.2 Effects on thrombus formation in a venous congestion model of FVIII neutralized cynomolgus monkeys (CTD 4.2.1.1.20, Study PHM[redacted]-0023)

At least 3 hours after intravenous administration of anti-FVIII neutralizing antibody (10 mg/kg), cynomolgus monkeys received emicizumab (3 mg/kg), FVIIa (120 μg/kg), or aPCC (100 U/kg) alone; emicizumab (3 mg/kg) and FVIIa (120 μg/kg) concomitantly; emicizumab (3 mg/kg) and aPCC (100 U/kg) concomitantly; or nothing (control) (n = 2-3 males/group). All agents were intravenously administered. In these monkeys, 1.5-hour congestion was induced by venous ligation. As a result, thrombus formation was not observed in the control group or emicizumab alone group. In the other dose groups, thrombus formation was observed. The thrombus weight in the emicizumab + FVIIa or emicizumab + aPCC group was not clearly higher than that in the corresponding single-agent group (FVIIa or aPCC alone group). In addition, data on platelet count, fibrinogen concentration, fibrin degradation product (FDP) concentration, and D-dimer before and after congestion did not suggest enhancement of coagulation or fibrinolysis in any group.

3.R Outline of the review conducted by PMDA

Based on the submitted data on primary pharmacodynamics, PMDA considers that emicizumab has binding affinity to FIXa and FX and is therefore expected to have a hemostatic effect. In addition, the submitted data on safety pharmacology are considered unlikely to raise safety concerns about emicizumab.

The clinical safety of concomitant use with FVIIa and aPCC investigated in the studies for pharmacodynamic drug interactions is discussed in Section 7.R.3.

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

The applicant submitted pharmacokinetics data from studies in cynomolgus monkeys. Emicizumab concentrations in plasma specimens were determined by ELISA. Anti-drug antibodies (ADAs) in plasma specimens were detected by electrochemical luminescence immunoassay and ELISA.

4.1 Absorption

4.1.1 Single-dose study

4.1.1.1 Single-dose study in cynomolgus monkeys (CTD 4.2.2.2-1, Study ADM[redacted]-0070)

Following a single intravenous administration of emicizumab at 6.0 mg/kg to cynomolgus monkeys (n = 3 males), plasma emicizumab concentrations were determined at a total of 15 time points that covered

baseline and a period from 15 minutes post-dose to Day 84. In addition, following a single subcutaneous administration of emicizumab at 0.060, 0.60, or 6.0 mg/kg to cynomolgus monkeys (n = 3 males/group), plasma emicizumab concentrations were determined at a total of 14 time points that covered baseline and a period from 2 hours post-dose to Day 84. Because plasma emicizumab concentrations decreased rapidly in response to ADA production, pharmacokinetic parameters were calculated from data only in animals without ADAs, as shown in Table 10 and Table 11.

The applicant's explanation about results from this study:
C_{max} and AUC_{inf} following subcutaneous administration of emicizumab increased proportionally to the dose, and $t_{1/2}$ did not differ among the doses. Bioavailability at 6.0 mg/kg (AUC_{inf} at subcutaneous dose/AUC_{inf} at intravenous dose) was 102.3%, showing no difference in the systemic exposure between intravenous and subcutaneous administration.

Table 10. Pharmacokinetic parameters of emicizumab following a single intravenous dose in cynomolgus monkeys (mean)

Dose (mg/kg)	No. of animals (n)	C_0 (μg/mL)	AUC_{inf} (μg·day/mL)	CL (mL/day/kg)	V_{ss} (mL/kg)	$t_{1/2}$ (day)
6.0	2[a]	142	1630	3.69	98.1	19.4

a Mean in 2 animals excluding 1 with ADAs

Table 11. Pharmacokinetic parameters of emicizumab following a single subcutaneous dose in cynomolgus monkeys (mean ± SD)

Dose (mg/kg)	No. of animals (n)	C_{max} (μg/mL)	AUC_{inf} (μg·day/mL)	T_{max} (day)	$t_{1/2}$ (day)
0.060	2[a]	0.6	25	3.00	26.5
0.60	3	5.1 ± 0.2	189 ± 45	5.00 ± 1.73	24.7 ± 8.1
6.0	3	45.7 ± 5.2	1670 ± 140	5.33 ± 2.89	23.6 ± 3.2

a Mean in 2 animals excluding 1 with ADAs

4.2 Distribution

Although a study for distribution of emicizumab has not been conducted, IgG is known to cross the placenta (*Birth Defects Res B Dev Reprod Toxicol.* 2009;86:328-44), and thus emicizumab, which is an IgG antibody, may cross the placenta. The applicant therefore explained that caution statements against use during pregnancy will be included in the package insert.

4.3 Metabolism

Because IgG antibody emicizumab is considered to be metabolized into peptides and amino acids as with endogenous IgG, no studies for metabolism have been conducted based on ICH-S6 (R1).

4.4 Excretion

Because IgG antibody emicizumab is considered to be metabolized into peptides and amino acids and then excreted as with endogenous IgG, no studies for excretion have been conducted based on ICH-S6 (R1). Although excretion of emicizumab into milk remains unknown, IgG is known to be excreted into milk (*Vaccine.* 2003;21:3374-6). The applicant therefore explained that caution statements against use in nursing women will be included in the package insert.

4.R Outline of the review conducted by PMDA

PMDA accepted the applicant's explanation on the absorption, distribution, metabolism, and excretion of emicizumab.

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant submitted toxicity data on of emicizumab from repeated-dose toxicity studies in cynomolgus monkeys, human tissue cross-reaction study, and *in vitro* study for cytokine release.

5.1 Single-dose toxicity

Although no single-dose toxicity study has been conducted, acute toxicity was evaluated based on results from repeated-dose toxicity studies. No emicizumab-related toxicity was observed at subcutaneous doses up to 30 mg/kg and intravenous doses up to 100 mg/kg.

5.2 Repeated-dose toxicity

5.2.1 Thirteen-week subcutaneous dose study in cynomolgus monkeys (CTD 4.2.3.2-2, Study TOX[redacted]-0057)

Cynomolgus monkeys (n = 5/sex/group, 3 years of age at baseline) subcutaneously received emicizumab at 0 (vehicle), 1, 6, or 30 mg/kg once weekly for 13 weeks. Three males and 3 females per group underwent necropsy 3 days after the last dose, and the remaining 2 males and 2 females per group underwent necropsy after a 13-week recovery period that followed the last dose. Hematology showed APTT shortening in all animals receiving emicizumab, but this change was reversible. Bleeding and inflammatory changes (e.g., mononuclear cell infiltration) were observed at the administration site mainly in the ≥6 mg/kg/week groups. These changes are not considered to be toxicity findings, because they are reversible changes commonly observed following subcutaneous administration of protein products. ADAs were detected in some animals in the 1 and 6 mg/kg/week groups; animals with ADAs had low plasma emicizumab concentrations. One female in the 1 mg/kg/week group showed high C-reactive protein (CRP) level after the first dose and then worsening of clinical signs, resulting in necropsy before the completion of study. This animal also had polyarthritis. This was a sporadic finding that was not observed in any other repeated-dose studies, and polyarthritis is known to occur spontaneously. Therefore, polyarthritis in the animal was considered to be an incidental change unrelated to emicizumab. Based on the above results, the no observed adverse effect level (NOAEL) was determined to be 30 mg/kg/week.

5.2.2 Twenty-six-week subcutaneous dose study in mature cynomolgus monkeys (CTD 4.2.3.2-3, Study TOX[redacted]-0007)

Cynomolgus monkeys (n = 5/sex/group, 4-6 years of age at baseline) subcutaneously received emicizumab at 0 (vehicle), 1, 6, or 30 mg/kg once weekly for 26 weeks. Three males and 3 females per group underwent necropsy 3 days after the last dose, and the remaining 2 males and 2 females per group underwent necropsy after a 13-week recovery period that followed the last dose. In all the emicizumab groups, bleeding and inflammatory changes such as mononuclear cell infiltration were observed at the administration site. These changes are not considered to be toxicity findings, because they are reversible changes commonly observed following subcutaneous administration of protein products. In this study, hematology did not show APTT shortening, but this different trend from the 13-week repeated-dose

toxicity study was caused by use of a different APTT reagent. The APTT reagent used in the 13-week repeated-dose toxicity study was considered to be more sensitive to the coagulation cascade in cynomolgus monkeys than that used in this study. ADAs were detected in some animals in all the emicizumab groups, and animals with ADAs had low plasma emicizumab concentrations. In addition, 1 male in the 6 mg/kg/week group underwent necropsy before the completion of study due to administration site swelling and development of ADAs. Acute vasculitis necrotizing with hemorrhagic changes and chronic vasculitis were observed at the administration site. It has been suggested that these changes were allergic reaction to xenogeneic protein and thus were not relevant to humans. In addition, low testis weight and immature genital organs were observed in 1 male in the 30 mg/kg/week group, but these changes were considered to fall within a range of inter-individual variability. Based on the above results, the NOAEL was determined to be 30 mg/kg/week.

5.2.3 Four-week intravenous dose study in cynomolgus monkeys (CTD 4.2.3.2-4, Study TOX[redacted]-0021)

Cynomolgus monkeys (n = 3/sex/group, + 2 animals to the vehicle group and 100 mg/kg/week group for evaluation of reversibility, 3-4 years of age at baseline) intravenously received emicizumab at 0 (vehicle), 10, 30, or 100 mg/kg once weekly for 4 weeks. Three males and 3 females per group underwent necropsy on the following day of the last dose, and 2 additional animals each in the vehicle group and 100 mg/kg/week group underwent necropsy after a 4-week recovery period that followed the last dose. Hematology showed APTT shortening, which was considered as the pharmacological effect, in all of the emicizumab groups, but this change was reversible. No other toxicological changes were observed, and no ADAs were detected. Polyarteritis was observed in 1 female in the 100 mg/kg/week group, but it was considered to be a spontaneous change. Based on the above results, the NOAEL was determined to be 100 mg/kg/week.

5.3 Genotoxicity

Because emicizumab is a humanized antibody with a large molecular weight, it is considered unlikely to have genotoxicity. No genotoxicity studies therefore have been conducted.

5.4 Carcinogenicity

Because emicizumab does not have cross-reactivity to rodents, no carcinogenicity studies have been conducted. Furthermore, no proliferative changes were observed in the repeated-dose toxicity studies in cynomolgus monkeys, and neither immunosuppression nor effects on the endocrine system were observed. Because no carcinogenicity concerns have been reported from clinical use of FVIII products, emicizumab, intended to be substituted for cofactor function of FVIII, is considered unlikely to have carcinogenicity.

5.5 Reproductive and developmental toxicity

The repeated-dose toxicity studies in cynomolgus monkeys showed that emicizumab had no particular effects on fertility. Emicizumab, if administered to normal animals, will cause reproductive and developmental toxicity (recurrent pregnancy loss) attributable to enhanced coagulation, and none of the study of fertility and early embryonic development and that for effects on pre-and postnatal development, including maternal function, have been conducted.

5.6 Local tolerance

No independent local tolerance studies have been conducted, but the local tolerance was evaluated in the 13-week and 26-week subcutaneous dose studies in cynomolgus monkeys. Emicizumab caused reversible and weak local irritation. In clinical studies, administration site reaction following treatment with emicizumab was also reported.

5.7 Other toxicity studies

5.7.1 Tissue cross-reactivity study (CTD 4.2.3.7.7-2, Study TOX[redacted]-0072)

A tissue cross-reactivity study of emicizumab (10 or 50 μg/mL) was conducted using human normal tissue frozen sections. Specific staining was observed in the liver (hepatocytes and Kupffer cells), adrenal gland (reticularis cells), thyroid gland (follicular epithelial cells), and bone marrow (myeloid cells). In these tissues, cytoplasm was stained. Based on the following pharmacological properties of emicizumab, relevant adverse drug reactions are considered unlikely to occur in humans.

- Although cytoplasm was stained, emicizumab, a humanized antibody, is unlikely to pass through the cell membrane and thus is unlikely to act directly in the cytoplasm *in vivo*.
- Emicizumab has neither an antigen-neutralizing nor cytotoxic effect.

5.7.2 *In vitro* study for cytokine release (CTD 4.2.3.7.7-3, Study TOX[redacted]-0083)

Human blood was incubated with emicizumab, panitumumab (anti-human epidermal growth factor receptor antibody, low risk control drug) or alemtuzumab (anti-human CD52 antibody, high risk control drug) at 0.1, 1, 10, or 100 μg/mL for 24 hours, followed by measurement of cytokines. The levels of cytokines induced by emicizumab were comparable to those induced by panitumumab.

5.R Outline of the review conducted by PMDA

PMDA has concluded that toxicity evaluation for emicizumab raises no particular problems.

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

6.1 Summary of biopharmaceutic studies and associated analytical methods

Emicizumab concentrations in plasma were determined by ELISA. ADAs were detected by electrochemical luminescence immunoassay or ELISA.

6.1.1 Bioavailability study (CTD 5.3.1.1-1, Study JP29574; Study period, April to October 2015)

A total of 60 healthy Japanese adult men aged ≥20 and <45 years received emicizumab as a single subcutaneous dose at 1 mg/kg or as a single intravenous dose at 0.25 mg/kg. Plasma emicizumab concentrations were determined at baseline and from 1 (intravenous dose) or 8 (subcutaneous dose) hours to 16 weeks post-dose. Pharmacokinetic parameters are shown in Table 12. Table 13 shows relative bioavailability following a single dose of the post-change product (Process B) to that following a single dose of the pre-change product (Process A), and relative bioavailability following a single dose of the post-change product to the upper arm or thigh to that following a single dose of the post-change

product to the abdomen. Table 14 shows absolute bioavailability following a subcutaneous dose of the post-change product.

The applicant's discussion about results from this study:
All the point estimates of the relative bioavailability fall within a range from 0.8 to 1.25. Neither manufacturing process nor administration site of the drug product is considered to have impacts on pharmacokinetics. Point estimates of absolute bioavailability fall within a range from 80.4% to 93.1%, indicating favorable absorption of emicizumab following subcutaneous dose irrespective of the administration site.

Table 12. Pharmacokinetic parameters following a single subcutaneous or intravenous dose (mean ± SD)

	Group A (N = 12)	Group B (N = 12)	Group C (N = 12)	Group D (N = 12)	Group E (N = 12)
Drug product	Pre-change product (Process A)	Post-change product (Process B)			
Dose	1 mg/kg	1 mg/kg	1 mg/kg	1 mg/kg	0.25 mg/kg
Route of administration	Subcutaneous (abdomen)	Subcutaneous (abdomen)	Subcutaneous (upper arm)	Subcutaneous (thigh)	Intravenous
C_{max} (μg/mL)	5.40 ± 0.91	6.26 ± 1.26	5.29 ± 0.96	7.56 ± 1.38	5.10 ± 0.51
AUC_{last} (day·μg/mL)	247 ± 56.8	253 ± 47.7	241 ± 40.4	284 ± 38.2	74.7 ± 10.9
AUC_{inf} (day·μg/mL)	271 ± 76.2	274 ± 53.3	260 ± 47.5	307 ± 45.6	79.2 ± 12.8

Table 13. Relative bioavailability (point estimates of geometric mean ratio [90% confidence interval (CI)])

	Product	Administration site	
	Post-change product/ pre-change product (Group B/Group A)	Upper arm/abdomen (Group C/Group B)	Thigh/abdomen (Group D/Group B)
Number of subjects[a]	23	21	23
C_{max}/Dose	1.199 [1.060, 1.355]	0.823 [0.718, 0.943]	1.168 [1.030, 1.324]
AUC_{last}/Dose	1.085 [0.942, 1.250]	0.931 [0.824, 1.051]	1.077 [0.979, 1.184]
AUC_{inf}/Dose	1.083 [0.920, 1.275]	0.926 [0.814, 1.053]	1.073 [0.969, 1.189]

a ADA-positive subjects (1 in Group B, 2 in Group C) were excluded from the study.

Table 14. Absolute bioavailability (point estimates of geometric mean ratio [90% CI])

	Abdomen (Group B/Group E)	Upper arm (Group C/Group E)	Thigh (Group D/Group E)
Number of subjects[a]	22	21	23
AUC_{inf}/Dose	0.868 [0.795, 0.948]	0.804 [0.712, 0.906]	0.931 [0.849, 1.022]

a ADA-positive subjects (1 in Group B, 2 in Group C, 1 in Group E) were excluded from the study.

6.2 Clinical pharmacology

The applicant submitted evaluation data on clinical pharmacology: results from a Japanese phase I study (CTD 5.3.3.1-1, Study ACE001JP), a Japanese phase I/II study (CTD 5.3.3.2-1, Study ACE002JP), and 2 global phase III studies (CTD 5.3.5.1-1, Study BH29884; CTD 5.3.5.2-1, Study BH29992).

6.2.1 Japanese phase I study (CTD 5.3.3.1-1, Study ACE001JP; Study period, August 2012 to April 2015)

This study consisted of 3 Parts (A, B, and C). In Parts A and B, healthy adult men aged ≥20 and <45 years (30 Japanese, 18 Caucasians) were given a single subcutaneous dose of emicizumab to investigate the pharmacokinetics. In these parts, Japanese subjects received emicizumab at 0.001, 0.01, 0.1, 0.3, or 1 mg/kg (6 per group), while Caucasian subjects received emicizumab at 0.1, 0.3, or 1 mg/kg (6 per

group). Plasma emicizumab concentrations were determined at baseline and from 8 hours to 24 weeks post-dose. Table 15 shows pharmacokinetic parameters of emicizumab. In all Japanese subjects receiving emicizumab 0.001 mg/kg, plasma emicizumab concentrations were below the lower limit of quantitation (0.05 μg/mL). Therefore the pharmacokinetic parameters in the Japanese emicizumab 0.001 mg/kg group were not calculated.

The applicant's explanation:
Pharmacokinetic parameters in the Japanese subjects were similar to those in the Caucasian subjects, and C_{max} and AUC_{inf} increased dose-proportionally.

Table 15. Pharmacokinetic parameters of emicizumab following a single subcutaneous dose to healthy Japanese or Caucasian adult men (mean ± SD)

	Japanese subjects (6 per group)				Caucasian subjects (6 per group)		
	0.01 mg/kg	0.1 mg/kg	0.3 mg/kg	1 mg/kg	0.1 mg/kg	0.3 mg/kg	1 mg/kg
C_{max} (μg/mL)	0.07 ± 0.01	0.66 ± 0.08	1.72 ± 0.38	5.92 ± 1.24	0.60 ± 0.08	2.12 ± 0.24	5.56 ± 0.81
t_{max} (day)[a]	14.1	12.0	10.1	10.1	12.6	7.0	8.53
AUC_{inf} (day·μg/mL)	-	30 ± 9	87 ± 18	266 ± 50	35 ± 13	112 ± 18	304 ± 79
$t_{1/2}$ (day)	-	28.3 ± 4.8	30.3 ± 4.1	29.0 ± 3.3	28.8 ± 10.4	34.4 ± 6.6	32.2 ± 6.7
CL/F (mL/day/kg)	-	3.51 ± 0.78	3.61 ± 0.85	3.91 ± 0.84	3.16 ± 0.93	2.75 ± 0.47	3.49 ± 0.93
V_d/F (mL/kg)	-	140 ± 24	156 ± 29	163 ± 36	121 ± 35	133 ± 15	156 ± 20

a Median

In Part C, 18 Japanese patients with severe hemophilia A aged ≥12 and <60 years (6 per group) subcutaneously received emicizumab once weekly for 12 weeks. The patients received emicizumab at 1 mg/kg for the first dose followed by 0.3 mg/kg for the subsequent doses (0.3 mg/kg/week group); at 3 mg/kg for the first dose followed by 1 mg/kg for the subsequent doses (1 mg/kg/week group); or at 3 mg/kg (3 mg/kg/week group). Plasma emicizumab trough levels reached the steady state at Week 12 in the 0.3 mg/kg/week and 1 mg/kg/week groups where the initial loading dose was given. On the other hand, in the 3 mg/kg/week group where the initial loading dose was not given, the trough levels did not reach the steady state during the 12-week treatment period.

6.2.2 Japanese phase I/II study (CTD 5.3.3.2-1, Study ACE002JP; Study period, ongoing since July 2013 [cut-off on September 30, 2016])

A total of 16 Japanese patients with severe hemophilia A aged ≥12 and <60 years (6 in the 0.3 mg/kg/week group, 5 in the 1 mg/kg/week group, 5 in the 3 mg/kg/week group) who completed Study ACE001JP, were enrolled in this study and continue to receive once-weekly subcutaneous treatment with emicizumab. In the 3 mg/kg group, plasma emicizumab trough levels did not reach the steady state at Week 12 as described above, but reached the steady state at Week 24. The trough levels at the steady state were 10.3 ± 4.5 μg/mL in the 0.3 mg/kg/week group, 29.9 ± 6.9 μg/mL in the 1 mg/kg/week group, and 120 ± 27 μg/mL in the 3 mg/kg/week group, indicating a dose-proportional increase.

6.2.3 Global phase III study (CTD 5.3.5.1-1, Study BH29884; Study period, ongoing since November 2015 [cut-off on October 25, 2016])

A total of 103 patients with hemophilia A aged ≥12 years (including 12 Japanese patients) who had a documented history of inhibitors at ≥5 BU/mL and had been treated with bypassing products received subcutaneous emicizumab at 3 mg/kg once weekly for 4 weeks, followed by once-weekly subcutaneous treatment at 1.5 mg/kg. The plasma emicizumab trough levels were 54.6 ± 14.3 μg/mL (98 patients) at

Week 4 and 52.0 ± 16.7 μg/mL (49 patients) at Week 24. In addition, the plasma emicizumab trough levels in Japanese patients were 55.3 ± 13.1 μg/mL (12 patients) at Week 4 and 45.7 ± 12.6 μg/mL (11 patients) at Week 24.

6.2.4 Global phase III study (CTD 5.3.5.2-1, Study BH29992; Study period, ongoing since July 2016 [cut-off on October 28, 2016])

A total of 20 patients with hemophilia A aged <12 years or aged 12 to 17 years but weighing <40 kg (including 5 Japanese patients) who had a documented history of inhibitors at ≥5 BU/mL and had been treated with bypassing products, received subcutaneous emicizumab at 3 mg/kg once weekly for 4 weeks, followed by once-weekly subcutaneous treatment at 1.5 mg/kg. The plasma emicizumab trough levels were 52.8 ± 8.7 μg/mL (20 patients) at Week 4 and 56.2 ± 16.3 μg/mL (11 patients) at Week 12. The plasma emicizumab trough levels in Japanese patients were 45.3 ± 4.9 μg/mL (5 patients) at Week 4 and 57.8 ± 16.1 μg/mL (4 patients) at Week 12.

The applicant's explanation:
Results from Studies BH29884 and BH29992 showed that changes in plasma emicizumab concentration over time in Japanese patients were similar to those in non-Japanese patients.

6.2.5 Population pharmacokinetics (CTD 5.3.3.5-1)

A population pharmacokinetic analysis was performed with a nonlinear mixed effect model (NONMEM version 7.2.0) using data on plasma emicizumab concentrations in patients with hemophilia A who received emicizumab in the Japanese phase I study (Study ACE001JP), Japanese phase I/II study (Study ACE002JP), or global phase III study (Studies BH29884 and BH29992) (1789 measurement points). The pharmacokinetics of emicizumab was described with a one-compartment model with first-order absorption and elimination processes. The analysis identified body weight, age, and albumin as covariates for CL/F as well as body weight, albumin, and race (black/African American) as covariates for distribution volume. Changes in plasma emicizumab concentration over time in patients who receive emicizumab at 1.5 mg/kg once weekly were simulated using the above model. A trough level at the steady state was estimated to be 52.8 ± 13.5 μg/mL.

6.R Outline of the review conducted by PMDA

6.R.1 ADAs

In the clinical studies, of 141 patients with hemophilia A who received emicizumab, 4 (2.8%) tested positive for ADAs (3 in the 0.3 mg/kg/week group and 1 in the 1 mg/kg/week group in Studies ACE001JP and ACE002JP). All the ADA positive patients, however, turned into ADA negative: the 3 patients in the 0.3 mg/kg/week group who were still receiving emicizumab tested negative at the last examination before data cut-off, and the 1 patient in the 1 mg/kg/week group who had discontinued treatment tested negative at the final observation point.

The applicant's explanation:
The pharmacokinetics, efficacy, and safety of emicizumab were not affected in any of these positive patients, indicating that the detected ADAs were not neutralizing antibodies, and therefore the ADAs had little clinical significance.

PMDA's view:
The currently available information does not suggest any clinical problem associated with ADAs. There are clinical studies currently ongoing, and attention should be continuously paid to effects of ADAs.

6.R.2 Dosage of emicizumab

The applicant's explanation about the dosage of emicizumab in phase III studies (Studies BH29884 and BH29992):
The population pharmacokinetic model was constructed using data on plasma emicizumab concentrations in 24 healthy Japanese adult men, 18 healthy Caucasian adult men, and 18 Japanese patients with hemophilia A who received emicizumab at 0.01 to 3 mg/kg in Study ACE001JP. In addition, an exposure-response model was constructed using data on bleeding episodes that required treatment in 18 Japanese patients with hemophilia A. As a result of simulations using these models, the following predictions were obtained:

- At least 50% of patients whose plasma emicizumab concentration remain at ≥45 μg/mL achieve an annualized bleeding rate (ABR) of 0.
- In patients aged ≥12 years, once-weekly subcutaneous treatment with emicizumab at 1.5 mg/kg result in the plasma emicizumab median trough level of ≥45 μg/mL at steady state.

The loading dose of emicizumab was 3 mg/kg administered subcutaneously once weekly for the first 4 weeks. This loading dose was selected to achieve a trough level ≥45 μg/mL as soon as possible after start of treatment with emicizumab at a dose not exceeding the highest dose (3 mg/kg/week) used in clinical studies. Based on the above, in Study BH29884 in patients aged ≥12 years, emicizumab was subcutaneously administered at 3 mg/kg once weekly for the first 4 weeks (loading dose), followed by once-weekly subcutaneous administration at 1.5 mg/kg (maintenance dose).

For patients aged <12 years, the target plasma concentration was defined as 45 μg/mL as with that for patients aged ≥12 years. Study BH29992 (conducted in patients aged <12 years) used the same starting dose as that used in Study BH29884, but allowed dose increase or adjustment during the study because the exposure in patients aged <12 years may be different from that in patients aged ≥12 years.

PMDA considers that the dosage used in Studies BH29884 and BH29992 is acceptable from a pharmacokinetic viewpoint. The appropriateness of dosage of emicizumab is discussed in Section 7.R.5, because it should be discussed based on the efficacy and safety data from the clinical studies as well as the above pharmacokinetic data.

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

The applicant submitted efficacy and safety evaluation data: results from a Japanese phase I study (CTD 5.3.3.1-1, Study ACE001JP), a Japanese phase I/II study (CTD 5.3.3.2-1, Study ACE002JP), and 2 global phase III studies (CTD 5.3.5.1-1, Study BH29884; CTD 5.3.5.2-1, Study BH29992). Table 16 lists the clinical studies.

Table 16. List of clinical studies

	Study ID (development phase)	Study population	No. of enrolled patients	Dosage regimen
Japan	ACE001JP (I)	Part A: Healthy Japanese adult men (aged ≥20 and <45 years) Part B: Healthy Caucasian adult men (aged ≥20 and <45 years) Part C: Japanese patients with severe hemophilia A (aged ≥12 and <60 years)	Part A: 40 Part B: 24 Part C: 18	Part A: Single subcutaneous administration of emicizumab at 0.001, 0.01, 0.1, 0.3 or 1 mg/kg, or placebo Part B: Single subcutaneous administration of emicizumab at 0.1, 0.3 or 1 mg/kg, or placebo Part C Step C-1: Once-weekly subcutaneous administration of emicizumab at 1 mg/kg for the first dose, followed by 0.3 mg/kg for the subsequent doses Step C-2: Once-weekly subcutaneous administration of emicizumab at 3 mg/kg for the first dose, followed by 1 mg/kg for the subsequent doses Step C-3: Once-weekly subcutaneous administration of emicizumab at 3 mg/kg
	ACE002JP (I/II)	Patients with hemophilia A who participated in Part C of Study ACE001JP.	16	Once-weekly subcutaneous administration of emicizumab at 0.3, 1, or 3 mg/kg
Global	BH29884 (III)	Patients with hemophilia A with inhibitors (aged ≥12 years)	Group A: 35 Group B: 18 Group C: 49 Group D: 7	Groups A, C, and D: Once-weekly subcutaneous administration of emicizumab at 3 mg/kg for the first 4 doses, followed by 1.5 mg/kg for the subsequent doses Group B: After 24-week observation period without emicizumab therapy, once-weekly subcutaneous administration of emicizumab at 3 mg/kg for the first 4 doses, followed by 1.5 mg/kg for the subsequent doses
	BH29992 (III)	Patients with hemophilia A with inhibitors (aged <12 years, or aged 12 to 17 years but weighing <40 kg)	20 (including 1 patient aged 12 years)	Once-weekly subcutaneous administration of emicizumab at 3 mg/kg for the first 4 doses, followed by 1.5 mg/kg for the subsequent doses

Outlines of the clinical studies are provided below. Pharmacokinetic data in each study are provided in Section “6.2 Clinical pharmacology.”

7.1 Phase I study

7.1.1 Japanese phase I study (CTD 5.3.3.1-1, Study ACE001JP; Study period, August 2012 to April 2015)

A clinical study was conducted to investigate the safety and pharmacokinetics of emicizumab in healthy Japanese and Caucasian adult men as well as Japanese patients with severe hemophilia A at 7 study sites in Japan.

This study consisted of 3 Parts. Study design for each Part is described below.

Part A was designed as a randomized, double-blind, placebo-controlled, dose-titration study in healthy Japanese adult men aged ≥20 and <45 years (target sample size; 8 subjects for each Step [6 in the emicizumab group, 2 in the placebo group], 40 subjects in total).

In Part A, subjects were to subcutaneously receive emicizumab at 0.001 (Step A-1), 0.01 (Step A-2), 0.1 (Step A-3), 0.3 (Step A-4), or 1 mg/kg (Step A-5), or placebo as a single dose. Subjects started with Step A-1. After the safety evaluation at 4 weeks post-dose, whether a subject can transfer to the next Step was determined. The observation period was 4 weeks for Steps A-1 and A-2, 16 weeks for Step A-3, 20 weeks for Step A-4, and 24 weeks for Step A-5.

Part B was designed as a randomized, double-blind, placebo-controlled, dose-titration study in healthy Caucasian adult men aged ≥20 and <45 years (target sample size; 8 subjects for each Step [6 in the emicizumab group, 2 in the placebo group], 24 subjects in total).

In Part B, subjects were to subcutaneously receive emicizumab at 0.1 (Step B-1), 0.3 (Step B-2) or 1 mg/kg (Step B-3), or placebo as a single dose. This Part was started with Step B-1 after the safety evaluation at 4 weeks post-dose in Step A-3. Whether a subject can transfer to Step B-2 was determined after the safety evaluation at 4 weeks post-dose in Step A-4 and B-1. Whether a subject can transfer to Step B-3 was determined after the safety evaluation at 4 weeks post-dose in Step A-5 and B-2. The observation period was 16 weeks for Step B-1, 20 weeks for Step B-2, and 24 weeks for Step B-3.

Part C was designed as an open-label, dose titration study in Japanese patients with severe hemophilia A aged ≥12 and <60 years (patients with inhibitors who had at least 6 bleeding episodes in 6 months before enrollment in the trial, and patients without inhibitors who had received FVIII products for a total of ≥150 days before enrollment and had received FVIII products regularly for 6 months before enrollment) (target sample size; 6 subjects for each Step, 18 subjects in total).

The patients were to subcutaneously receive emicizumab once weekly at 1 mg/kg for the first dose, followed by 0.3 mg/kg for the subsequent doses (Step C-1); at 3 mg/kg for the first dose, followed by 1 mg/kg for the subsequent doses (Step C-2); or at 3 mg/kg (Step C-3). Emicizumab was administered for 12 weeks. In Part C, patients started with Step C-1 after the safety evaluation at 4 weeks post-dose in Step A-5, and whether a patient can transfer to the next Step was determined after the safety evaluation at ≤12 weeks post-dose. The post-dose follow-up period was 28 weeks for Steps C-1, 32 weeks for Step C-2, and 36 weeks for Step C-3.

All of the 82 subjects who were enrolled and treated with the study drug (40 in Part A, 24 in Part B, 18 in Part C) were included in the safety analysis population.

For the safety, no adverse events led to death in Parts A to C.

In Part A, during the observation period, adverse events were reported by 26.7% (8 of 30) of subjects in the emicizumab group (9 events: 3 events of nasopharyngitis, 2 events of stomatitis, 1 event each of diarrhoea, pyrexia, erythema of eyelid, and seasonal allergy), and 20.0% (2 of 10) of subjects in the placebo group (2 events: 1 event each of nasopharyngitis and headache), but all the events resolved. Neither serious adverse events nor adverse events leading to study discontinuations occurred.

In Part B, during the observation period, adverse events were reported by 27.8% (5 of 18) of subjects in the emicizumab group (6 events: 1 event each of abdominal pain upper, bite, syncope, blood bilirubin increased, bilirubin conjugated increased, and nasopharyngitis), and 33.3% (2 of 6) of subjects in the placebo group (4 events: 1 event each of diarrhoea, excoriation, headache, and haemorrhage subcutaneous), but all the events resolved. Blood bilirubin increased and bilirubin conjugated increased in the emicizumab group as well as haemorrhage subcutaneous in the placebo group were assessed to be related to the study drug. Neither serious adverse events nor adverse events leading to study discontinuations occurred.

In Part C, during the follow-up period, 51 adverse events occurred in 88.9% (16 of 18) of subjects. Adverse events reported by ≥2 subjects included nasopharyngitis in 3 subjects as well as myalgia, erythema, contusion, excoriation, tongue injury, and injection site haematoma in 2 subjects each, and these events were not dose-dependent. Adverse drug reactions were reported by 33.3% (6 of 18) of subjects (12 events: 4 events of injection site rash, 2 events of injection site erythema, and 1 event each of CRP increased, diarrhoea, blood creatine phosphokinase increased, malaise, injection site pruritus, and injection site discomfort), but all the adverse drug reactions were mild in severity and resolved except for diarrhoea, which was reported as "not resolved." In 1 subject who experienced injection site erythema, erythema occurred at all the first to third injection sites simultaneously after the third dose of emicizumab, and redness occurred at the injection sites after the fourth dose. On Day 29, emicizumab was discontinued. This subject experienced a serious adverse event of haemophilia (left hip joint bleeding due to haemophilia) during the follow-up period after discontinuation of the study drug (Day 173), but a causal relationship of this event to emicizumab was ruled out, and it resolved.

7.2 Phase I/II study

7.2.1 Japanese phase I/II study (CTD 5.3.3.2-1, Study ACE002JP; Study period, ongoing since July 2013 [cut-off on September 30, 2016])

An open-label, extension study was conducted in patients with severe hemophilia A who had participated in Part C of Study ACE001JP, to investigate the safety and potential efficacy of long-term treatment with emicizumab at 6 study sites in Japan.

Of the 18 subjects who had participated in Part C of Study ACE001JP, 16 subjects (6 in the 0.3 mg/kg/week group, 5 in the 1 mg/kg/week group, 5 in the 3 mg/kg/week group) were included in this study. A total of 18 subjects including 2 subjects who had participated only in Part C of Study ACE001JP were included in the safety analysis population.

A total of 15 subjects who extended the treatment from Week 12 in Part C of Study ACE001JP (5 in the 0.3 mg/kg/week group, 5 in the 1 mg/kg/week group, 5 in the 3 mg/kg/week group) continued treatment at the same dose. In addition, in 1 subject who had completed the 12-week treatment (0.3 mg/kg/week) in Part C of Study ACE001JP and resumed emicizumab after the 28-week follow-up period, the dose was increased to 1 mg/kg/week (3 mg/kg for the first dose after resumption) in resumed treatment. Then, step-wise dose increases (from 0.3 mg/kg/week to 1 mg/kg/week [3 mg/kg for the first dose in the increased-dose treatment], or from 1 mg/kg/week to 3 mg/kg/week) were allowed corresponding to the patient condition.

Until the data cut-off date, 3 subjects in the 0.3 mg/kg/week group increased the dose to 1 mg/kg/week, and of these, 2 subjects increased it to 3 mg/kg/week. In addition, 1 subject in the 1 mg/kg/week group increased the dose to 3 mg/kg/week.

For the efficacy, the ABR of bleeding episodes requiring a blood coagulation factor product (FVIII product or bypassing product) was evaluated. Table 17 shows the ABR in each group.

Table 17. ABR of bleeding episodes requiring a blood coagulation factor product (FVIII product or bypassing product) (safety analysis population[a])

	0.3 mg/kg/week			1 mg/kg/week			3 mg/kg/week		
	N	Median	Range	N	Median	Range	N	Median	Range
Pre-treatment 6 months (prior to enrollment in Study ACE001JP)	6	32.46	(8.1, 77.1)	6	18.26	(10.1, 38.6)	6	15.22	(0, 32.5)
From the first dose to Week 12	6	4.35	(0, 59.5)	6	0	(0, 4.3)	6	0	(0, 4.2)
From the first dose to data cut-off date	6	1.27	(0, 59.5)	9[b]	0.68	(0, 29.1)	9[b]	0	(0, 10.0)

The ABR was calculated according to the following formula: For the pre-treatment period, number of bleeding episodes in 6 months prior to the treatment with emicizumab (enrollment in Study ACE001JP) × 2.029; and for a period of treatment with emicizumab, (number of bleeding episodes after start of the treatment at the present dose) / (number of days from start of the treatment at the present dose to data cut-off date, to the day before start of the treatment at an increased dose, or to the day 1 week after discontinuation of emicizumab) × 365.25.

a Including subjects who were not included in this study but participated in Part C of Study ACE001JP

b For 4 subjects in whom the dose was increased, the ABR was calculated at each dose level.

For the safety, 195 adverse events occurred by the data cut-off date in 100% (16 of 16) of the subjects who were included in the safety analysis population and transferred to this study.

Adverse drug reactions were reported by 31.3% (5 of 16) of subjects (23 events: 18 events of injection site erythema, 2 events of injection site pruritus, and 1 event each of nausea, injection site induration, and injection site pain), but all the adverse drug reactions were mild in severity and resolved except for 1 event of injection site pruritus, which was reported as “not resolved.” Serious adverse events were reported by 4 subjects (4 events: 1 event each of haemophilia [subcutaneous haemorrhage of tongue tip due to haemophilia], mesenteric haematoma, appendicitis, and laceration), but a causal relationship to the study drug was ruled out for all the events. All the events resolved.

7.3 Phase III studies

7.3.1 Global phase III study (CTD 5.3.5.1-1, Study BH29884; Study period, ongoing since November 2015 [cut-off on October 25, 2016])

An open-label study was conducted at 43 study sites in 14 countries including Japan, to investigate the efficacy, safety, and pharmacokinetics of emicizumab in patients with hemophilia A aged ≥12 years who had a documented history of inhibitors at ≥5 BU/mL and had been treated with bypassing products.

Subjects who had been using bypassing products to treat bleeding episodes were stratified according to the number of bleeding episodes in the last 24 weeks prior to enrollment (<9 and ≥9 episodes) and randomized to Group A or B at the ratio of 2:1 (target sample size, 34 subjects in Group A, 17 subjects in Group B). In addition, subjects who had been periodically treated with bypassing products were assigned to Group C (target sample size, 30-50 subjects). After the completion of assignment to Groups A to C, subjects were assigned to Group D.

In Groups A, C, and D, subjects were to subcutaneously receive emicizumab once weekly at 3 mg/kg for the first 4 doses, followed by 1.5 mg/kg for the subsequent doses. In Group B, subjects were to be initially subjected to observation (for 24 weeks) without emicizumab therapy and then were to subcutaneously receive emicizumab once weekly at 3 mg/kg for the first 4 doses, followed by 1.5 mg/kg for the subsequent doses. A bypassing product was to be administered to subjects experiencing a bleeding episode requiring treatment during the study period.

This study enrolled 109 subjects (35 in Group A, 18 in Group B, 49 in Group C, 7 in Group D) (of these, 12 Japanese subjects [5, 1, 6, 0]). The safety analysis population 1 included 108 subjects who received ≥1 dose of emicizumab in Groups A, C, and D or were subjected to observation without emicizumab therapy in Group B (34, 18, 49, 7) (of these, 12 Japanese subjects [5, 1, 6, 0]). The remaining 1 subject in Group A was excluded because he discontinued the study before the start of emicizumab therapy. The safety analysis population 2 included 103 subjects who received ≥1 dose of emicizumab during the study period (34, 13, 49, 7) (of these, 12 Japanese subjects [5, 1, 6, 0]). All of the 53 subjects who were assigned to Group A or B (35 in Group A, 18 in Group B) (of these, 6 Japanese subjects [5, 1]) were included in the intent-to-treat (ITT) population, which also served as the primary efficacy analysis population.

As of the data cut-off date, the median observation period (range) was 29.3 (0.1, 48.9) weeks in Group A, 19.1 (6.9, 45.3) weeks in Group C, and 6.1 (4.0, 14.9) weeks in Group D, and the median observation period without emicizumab therapy in Group B was 24.1 (23.0, 26.0) weeks.

The primary efficacy endpoint was the ABR of bleeding episodes requiring treatment in the ITT ([number of bleeding episodes during the efficacy analysis period / the total number of days of the efficacy analysis period] × 365.25). A significant difference in ABR between Groups A and B was indicated (Table 18). In the Japanese subjects, the median ABR (range) was 3.3 (0.00, 6.52) in Group A (5 subjects) and 15.1 in Group B (1).

Table 18. Comparison of ABR of bleeding episodes requiring treatment between groups (ITT)

	Group A (N = 35)	Group B (N = 18)[b]
Median ABR (range)	0.0 (0.00, 33.72)	18.8 (0.00, 77.80)
ABR (95% CI)[a]	2.9 [1.69, 5.02]	23.3 [12.33, 43.89]
ABR group ratio (Group A/Group B) (95% CI)[a]	0.13 [0.057, 0.277]	
P value[a]	<0.0001	

a Negative binomial regression model in which the dose group and the number of bleeding episodes (<9, ≥9) in the last 24 weeks prior to enrollment were fixed effects, and logarithm of the evaluation period was offset

b Observation period without emicizumab therapy

The median ABR of bleeding episodes requiring treatment (range) was 0.0 (0.00, 98.72) in Group C (49 subjects) and 0.0 (0.00, 65.22) in Group D (7 subjects), and that in the 6 Japanese subjects in Group C was 0.0 (0.00, 5.11).

For the safety, 198 adverse events occurred in 70.9% (73 of 103) of subjects in the safety analysis population 2 by the data cut-off date. Adverse events reported by ≥5 subjects are shown in Table 19.

Table 19. Adverse events reported by ≥5 subjects

	Safety analysis population 2								Safety analysis population 1	
	Group A (N = 34)		Group B (N = 13)		Group C (N = 49)		Group D (N = 7)		Group B (N = 18)[a]	
	No. of subjects (%)	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	No. of events
Injection site reaction	8 (23.5)	15	1 (7.7)	1	5 (10.2)	11	1 (14.3)	1	0	0
Headache	3 (8.8)	3	1 (7.7)	1	6 (12.2)	7	2 (28.6)	2	0	0
Upper respiratory tract infection	7 (20.6)	9	0	0	2 (4.1)	2	0	0	3 (16.7)	3
Arthralgia	2 (5.9)	3	1 (7.7)	1	3 (6.1)	6	0	0	0	0
Fatigue	3 (8.8)	3	1 (7.7)	1	2 (4.1)	2	0	0	0	0
Diarrhoea	1 (2.9)	1	1 (7.7)	1	3 (6.1)	3	0	0	0	0
Pyrexia	0	0	2 (15.4)	2	3 (6.1)	3	0	0	1 (5.6)	1

a Data for Group B in the safety analysis population 1 were based on information during the observation period without emicizumab therapy.

Adverse drug reactions were reported by 22.3% (23 of 103) of subjects (13 in Group A, 1 in Group B, 9 in Group C, 0 in Group D) in the safety analysis population 2 (42 events: 24 events of injection site reaction, 3 events of hair growth abnormal, 2 events each of thrombotic microangiopathy and fatigue, and 1 event each of abdominal pain, cavernous sinus thrombosis, decreased appetite, dehydration, general physical health deterioration, nausea, petechiae, skin lesion, skin necrosis, throat irritation, and thrombophlebitis superficial).

In total, 12 serious adverse events occurred in 9 subjects in the safety analysis population 2 (5 events in 4 subjects in Group A [1 event each of thrombotic microangiopathy, skin necrosis, thrombophlebitis superficial, iron deficiency anaemia, and muscle haemorrhage]; 1 event in 1 subject in Group B [haemarthrosis]; 6 events in 4 subjects in Group C [1 event each of sepsis, thrombotic microangiopathy, haematuria, headache, gastric ulcer haemorrhage, and cavernous sinus thrombosis]). Of these, serious adverse drug reactions were 2 events of thrombotic microangiopathy and 1 each of skin necrosis, thrombophlebitis superficial, and cavernous sinus thrombosis, but all the serious adverse drug reactions were reported to have resolved or be resolving. One subject who experienced thrombotic microangiopathy and 1 subject who experienced skin necrosis and thrombophlebitis superficial concurrently (both in Group A) discontinued the study. In Group B in the safety analysis population 1, 7 serious adverse events (2 events of haemarthrosis, and 1 event each of gastrointestinal haemorrhage, subdural haemorrhage, urinary tract infection, device related infection, and device related sepsis) occurred in 4 subjects during the observation period without emicizumab therapy.

For the safety in 12 Japanese subjects, 24 adverse events occurred in 9 subjects by the data cut-off date. In addition, 4 episodes of adverse drug reactions (injection site reaction) occurred in 1 subject in Group A. None of the Japanese subjects experienced serious adverse events, adverse events leading to treatment discontinuation, thromboembolic events, or thrombotic microangiopathy.

After the data cut-off date, 1 subject in Group C who had rectal haemorrhage and thrombotic microangiopathy concurrently died of rectal haemorrhage as a consequence of declining transfusion based on his own creed.

7.3.2 Global phase III study in children (CTD 5.3.5.2-1, Study BH29992; Study period, ongoing since July 2016 [cut-off on October 28, 2016])

An open-label study was conducted at 12 study sites in 6 countries including Japan, to investigate the efficacy, safety, and pharmacokinetics of emicizumab in pediatric patients with hemophilia A aged <12 years or aged 12 to 17 years but weighing <40 kg who had a documented history of inhibitors at ≥5 BU/mL and had been treated with bypassing products (target sample size, minimum 20 subjects, maximum 60 subjects).

In this study, enrollment was planned as follows: It is started with subjects aged ≥2 and <12 years; when a total of 10 subjects have received emicizumab for at least 12 weeks, interim data evaluation is performed; after completion of the evaluation, enrollment of subjects aged <2 years is started.

Subjects were to subcutaneously receive emicizumab once weekly at 3 mg/kg for the first 4 doses, followed by 1.5 mg/kg for the subsequent doses. Emicizumab was administered for 52 weeks. A bypassing product was to be administered to subjects experiencing a bleeding episode requiring treatment during the study period.

Twenty subjects (19 subjects aged <12 years [including 4 Japanese subjects], 1 subject aged 12 years who weighed <40 kg [Japanese subject]) were enrolled by the data cut-off date. All of the 20 subjects who received ≥1 dose of emicizumab were included in the safety analysis population. Of these, 19 subjects aged <12 years were included in the efficacy analysis population. As of the data cut-off date, 11 subjects received emicizumab for at least 12 weeks, and the median observation period (range) was 12.1 (7.1, 14.1) weeks.

For the efficacy, 1 bleeding episode requiring treatment occurred in 1 of 19 subjects by the data cut-off date. The concerned subject was Japanese.

For the safety, 43 adverse events occurred in 70.0% (14 of 20) of the subjects by the data cut-off date. Adverse events reported by ≥2 subjects in the safety analysis population included nasopharyngitis and injection site reaction in 3 subjects each, and upper respiratory tract infection, pyrexia, myalgia, and anaemia in 2 subjects each. Adverse drug reactions occurred in 15.0% (3 of 20) of the subjects (9 events of injection site reaction). Serious adverse events occurred in 3 subjects (3 events: catheter site infection, mouth haemorrhage, and appendicitis in 1 subject each), but a causal relationship to emicizumab was ruled out for all of the events. All of the events resolved. No patients died or experienced adverse events leading to treatment discontinuation, thromboembolic events, or thrombotic microangiopathy.

For the safety in Japanese subjects, 14 adverse events occurred in 3 of 5 subjects by the data cut-off date, but no adverse drug reactions occurred. One serious adverse event (mouth haemorrhage) occurred in 1 subject, but a causal relationship between the event and emicizumab was ruled out, and it resolved.

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

Emicizumab is developed as a drug only indicated for periodic prophylaxis to prevent bleeding, but not for hemostasis in the case of bleeding or surgery, although it is intended to be substituted for FVIII function. For patients with hemophilia A with inhibitors, the following are similar in and outside Japan: epidemiologic characteristics, pathological conditions of bleeding tendency, and therapeutic concepts of treatment of bleeding (use of bypassing products and inhibitor-neutralizing therapy) and treatment during nonbleeding time (immune tolerance induction therapy and periodic use of bypassing products to prevent bleeding). This suggests that effects of intrinsic and/or extrinsic ethnic factors on the efficacy and safety of emicizumab are considered insignificant. Accordingly, the efficacy of emicizumab was evaluated based on data from Study BH29884 (which was a global study and selected as the pivotal study) and Study BH29992 (which included children <12 years old). More specifically, reduction in bleeding tendency by periodical treatment with emicizumab was evaluated. The safety was evaluated based on adverse events in all of the clinical studies that were included in the submitted evaluation data. The safety information collected after the data cut-off date from the ongoing Studies ACE002JP, BH29884, and BH29992, is not included in the data package for the present application; however, this information (e.g., adverse events) was also reviewed.

7.R.2 Efficacy

7.R.2.1 Efficacy of emicizumab

The applicant's explanation about the efficacy of emicizumab:

It is ethically unacceptable to use placebo as a control in Study BH29884 because of the seriousness of bleeding in patients with hemophilia A with inhibitors. When the study was planned, periodic use of bypassing products was not positioned as a standard of care. Therefore, Study BH29884 (the pivotal study) was designed to randomly assign patients who were receiving bypassing products for bleeding episodes to a group receiving periodic treatment with emicizumab (Group A) or a group not receiving emicizumab (Group B), to compare the ABR in Groups A and B. A significant difference was detected in ABR of bleeding episodes requiring treatment, the primary endpoint in Study BH29884, between Group A and Group B during the observation period without emicizumab therapy (Table 18). Patients who had periodically received bypassing products at baseline were included in a group switching from the periodic use of bypassing products to that of emicizumab (Group C) to investigate the ABR. In Group C, the median ABR of bleeding episodes requiring treatment (range) was 0.0 (0.00, 98.72), which was as low as that in Group A (0.0 [range; 0.00, 33.72]).

The applicant determined that the above results demonstrated the efficacy of emicizumab.

PMDA accepted the applicant's explanation.

7.R.2.2 Consistency of results between the entire study population and Japanese population

PMDA's view on consistency of efficacy between the entire study population and Japanese population:

Although only 12 Japanese subjects were included in Study BH29884, the ABR of bleeding episodes requiring treatment, the primary efficacy endpoint, was similar in the entire study population and

Japanese population (Table 20). In addition, Study ACE002JP in 16 Japanese patients with hemophilia A showed that emicizumab reduced the ABR (Table 17).

Based on the above, PMDA has concluded that emicizumab is expected to be effective in Japanese patients as well.

Table 20. ABR of bleeding episodes requiring treatment in Study BH29884

	Group A			Group B			Group C		
	N	Median	(range)	N	Median	(range)	N	Median	(range)
Entire study population	35	0.0	(0.00, 33.72)	18	18.8	(0.00, 77.80)	49	0.0	(0.00, 98.72)
Japanese population	5	3.3	(0.00, 6.52)	1	15.1	-	6	0.0	(0.00, 5.11)

ITT for Group A and Group B (observation period without emicizumab therapy); all the subjects who received emicizumab for Group C.

7.R.3 Safety

Serious adverse events occurring by the data cut-off date were reported by 1 subject in Study ACE001JP (1 event, haemophilia [left hip joint bleeding due to haemophilia]), by 4 subjects in Study ACE002JP (4 events: 1 event each of haemophilia [subcutaneous haemorrhage of tongue tip due to haemophilia], mesenteric haematoma, appendicitis, and laceration), by 9 subjects in Study BH29884 (12 events: 2 events of thrombotic microangiopathy, and 1 event each of skin necrosis, thrombophlebitis superficial, iron deficiency anaemia, muscle haemorrhage, haemarthrosis, sepsis, haematuria, headache, gastric ulcer haemorrhage, and cavernous sinus thrombosis), and by 3 subjects in Study BH29992 (3 events: 1 event each of catheter site infection, mouth haemorrhage, and appendicitis). Of these, a causal relationship to emicizumab could not be ruled out for 5 events in 4 subjects in Study BH29884 (2 events of thrombotic microangiopathy, and 1 event each of skin necrosis, thrombophlebitis superficial, and cavernous sinus thrombosis).

Neither shock nor anaphylaxis occurred in any clinical study. In Study BH29884, 2 adverse events (1 event each of cough and flushing) suspected of systemic hypersensitivity reactions occurred, but such a suspect was ruled out. Both events resolved without treatment, and their causal relationship to emicizumab was ruled out.

Incidences of adverse events by age were 67.6% (48 of 71) of subjects aged ≥18 years in Study BH29884, 78.1% (25 of 32) of subjects aged ≥12 and <18 years in Study BH29884, and 70.0% (14 of 20) of subjects in Study BH29992, which included subjects aged <12 years (including patients aged 12-17 years who weighed <40 kg); the incidences were similar irrespective of age. No adverse events specific to subjects aged <12 years were found.

Based on the submitted clinical study results, PMDA considers that the safety profile does not differ between children and adults. All of the 5 serious adverse events for which a causal relationship to emicizumab could not be ruled out, were thromboembolic events or thrombotic microangiopathy. These events are discussed in the following section.

7.R.3.1 Thromboembolic events and thrombotic microangiopathy due to concomitant use of bypassing products

The applicant's explanation about thromboembolic events and thrombotic microangiopathy in Study BH29884:

By the data cut-off date, 2 subjects experienced thromboembolic events (skin necrosis and thrombophlebitis superficial; cavernous sinus thrombosis), and 2 subjects experienced thrombotic microangiopathy while receiving periodic treatment with emicizumab. All were serious adverse events and their causal relationships to emicizumab could not be ruled out. All of the adverse events occurred in association with use of bypassing products. Table 21 shows use status of the bypassing products.

Subject 1 underwent surgical debridement for skin necrosis. Subject 3 received treatment such as plasma exchange and hemodialysis. Both subjects were reported to have recovered or be recovering, but discontinued the study. Subjects 2 and 4 recovered without use of anti-coagulation drugs, plasma exchange, or hemodialysis, and resumed treatment with emicizumab to continue the study. By the data cut-off date, neither thromboembolic events nor thrombotic microangiopathy for which a causal relationship to emicizumab could not be ruled out occurred in any clinical study other than Study BH29884.

Table 21. Use status of bypassing products in subjects who experienced thromboembolic events or thrombotic microangiopathy

Subject (group)	Adverse event	Date of onset	Date of the last dose of emicizumab	Purpose of bypassing products	Dose of aPCC product (date of treatment, unit/kg)	Dose of rFVIIa product (date of treatment, μg/kg)
1 (A)	Skin necrosis Thrombophlebitis superficial	Day 147 Day 149	Day 147	Idiopathic knee joint bleeding	Day 145: 101 × 1	No treatment
				Idiopathic shin muscle bleeding	Day 146: 101 × 1	No treatment
2 (C)	Cavernous sinus thrombosis	Day 134	Day 130	Traumatic knee joint bleeding	Day 131: 83 × 1 Day 132: 86 × 3 Day 133: 86 × 2, 104 × 1 Day 134: 87 × 1	No treatment
3 (A)	Thrombotic microangiopathy	Day 50	Day 50	Traumatic knee joint bleeding	Day 48: 94 × 1	No treatment
				Idiopathic elbow joint bleeding	Day 49: 94 × 1	No treatment
				Low back pain (considered by the subject as a symptom of spontaneous haemorrhage)	Day 50: 94 × 2	Day 50: 85 × 2
				CV catheter placement	No treatment	Day 52: 85 × 3
				CV catheter replacement	No treatment	Day 56: 94 × 1 Day 65: 87 × 1
4 (C)	Thrombotic microangiopathy	Day 222	Day 218	Traumatic ankle joint bleeding	Day 218: 74 × 1 Day 219: 74 × 2 Day 220: 74 × 2	No treatment
5[a] (C)	Thrombotic microangiopathy	Day 243	Day 238	Rectal haemorrhage	Day 240: 98 × 1, 65 × 2 Day 241: 65 × 3 Day 242: 65 × 3 Day 243: 65 × 3	Day 238: 87 × 3 Day 239: 87 × 5 Day 240: 87 × 3

a Subject 5 experienced the event after data cut-off date.

All of the 4 subjects who experienced thromboembolic events or thrombotic microangiopathy by the data cut-off date received multiple doses of aPCC products on consecutive days concomitantly with

emicizumab (Subjects 1-4 in Table 21). For subjects who received aPCC products for any purpose in Study BH29884, the relationship between cumulative dose of the aPCC products during a specified period and onset of thromboembolic events or thrombotic microangiopathy was investigated. Multiple doses of aPCC products led to accumulation of the ingredients (*Critical Care.* 2011;15:201-9), and 1 treatment event was defined as a period from the start of aPCC therapy to the time point at which aPCC therapy has been absent for 36 hours. The plasma emicizumab concentrations were low during the first 7 days after the first dose of emicizumab and 30 days after discontinuation of emicizumab. Therefore these periods were not included in the treatment event. The results showed that aPCC products were used in 65 treatment events in 18 subjects. Table 22 shows the mean daily dose of aPCC products and the total number of treatment events by treatment period.

Table 22. Mean daily dose of aPCC products and total number of treatment events by treatment period

Treatment period with aPCC products	Mean daily dose of aPCC products (unit/kg/day)				Total number of treatment events by treatment period
	<50	50-100	101-150	>150	
<24 hours	1	44	7	5	57
≥24 and <48 hours	0	1	1[d]	0	2
≥48 and <72 hours	0	0	3[a,c]	1[b]	4
≥72 and <96 hours	0	0	2	0	2
≥96 hours	0	0	0	0	0
Total number of treatment events by mean daily dose	1	45	13	6	65

a, Subject 3; b, Subject 2; c, Subject 4; d, Subject 1

The above results suggest that concomitant use of emicizumab with aPCC products at high cumulative doses potentially increases a risk of thromboembolic events/thrombotic microangiopathy. A similar analysis was also performed for rFVIIa products, but there was no treatment event related to thromboembolic events/thrombotic microangiopathy in which only rFVIIa products were administered concomitantly. A risk of thromboembolic events/thrombotic microangiopathy in patients who received emicizumab and aPCC products concomitantly was higher than that in patients who received emicizumab and rFVIIa products concomitantly. The following reason for the higher risk is considered: FIX, FIXa, and FX contained in aPCC products can augment cofactor function of emicizumab, which is expected to be substituted for FVIII to enhance FIXa-mediated activation of FX. On the other hand, rFVIIa products do not contain FIX, FIXa, or FX and exert a blood coagulation enhancement activity only based on the effect of FVIIa. rFVIIa products are therefore considered to have a lower risk of thromboembolic events/thrombotic microangiopathy than aPCC products.

The applicant considered that concomitant use of emicizumab with aPCC products should be avoided to suppress the risk of thromboembolic events/thrombotic microangiopathy, and therefore added the following provisions about use of bypassing products (3 types of products approved in Japan, including aPCC, FVIIa/FX, and rFVIIa products) to protocols of Studies BH29884, BH29992, and ACE002JP, which were ongoing then. In addition, the number of treatment events with FVIIa/FX products was limited. Therefore the risk of thromboembolic events/thrombotic microangiopathy in patients receiving emicizumab and FVIIa/FX products concomitantly remains unknown. Nevertheless FVIIa/FX products contain FX on which emicizumab acts and thus may augment the cofactor function of emicizumab. FVIIa/FX products were therefore handled in the same manner as aPCC products.

- For treatment of bleeding during treatment with emicizumab, rFVIIa products should be used, and the other bypassing products such aPCC and FVIIa/FX products should be avoided.
- If a bypassing product is used to treat bleeding during treatment with emicizumab, the initial dose of the bypassing product should be the minimum dose necessary for hemostasis (the approved minimum dose), and the subject and physician should discuss how to use bypassing products in advance.
- If a bypassing product is used twice or more, it should be used under supervision of a physician for any type of the product.
- For subjects treated with a bypassing product, laboratory test parameters related to thromboembolic events and thrombotic microangiopathy should be monitored.

Furthermore, subjects were instructed to always carry a card that described precautions for concomitant use of each of the above bypassing products, how to identify thromboembolic events, and procedures for receiving emergency care. Because subjects may receive emergency care at medical institutions other than the study site, the card also included the following information for healthcare professionals not involved in the study: Emicizumab may cause thromboembolic events/thrombotic microangiopathy; emicizumab affects laboratory test results on the coagulation system such as APTT; and the study site (investigator) should be informed of the care provided outside of the study site.

In Study BH29884, subjects treated with aPCC products during treatment with emicizumab decreased after addition of the above provisions and safety measures (after the data cut-off date):

Before: 26 of 103 subjects (13 used aPCC product alone, 13 used aPCC product + rFVIIa product).
After: 7 of 105 subjects (3 used aPCC product alone, 4 used aPCC product + rFVIIa product).

Serious thrombotic microangiopathy occurred in 1 of 7 subjects who used aPCC products after addition of the provisions. This subject (Table 21, Subject 5) received bypassing products (aPCC products) at a daily dose >150 U/kg for 4 consecutive days (≥72 and <96 hours) during treatment of the serious adverse event (rectal haemorrhage) that led to death. The fatal outcome was probably caused by the following reasons: (a) the location of rectal haemorrhage could not be identified, which prevented the surgical treatment; (b) transfusion was not implemented at the request of the subject.

Even after addition of provisions about use of bypassing products, thrombotic microangiopathy occurred following concomitant use of aPCC products. The following actions were therefore taken:

- The study sites were re-informed of the provisions.
- The protocol was revised to clarify the following instructions:
  (a) Before self-injecting an rFVIIa product, the subject should consult the physician at the study site about the necessity of rFVIIa therapy and its dose.
  (b) If use of an aPCC product or FVIIa/FX product is inevitable, the subject must use the bypassing product under supervision of the physician from the first dose.

After the revision, no additional thromboembolic events/thrombotic microangiopathy have occurred (as of December 2017).

To ensure thoroughly that the provisions about use of bypassing products established in the clinical studies are followed even in the post-marketing settings, the following post-marketing safety measures are planned:

- Requirements for medical institutions and physicians are established to ensure that emicizumab is properly used by physicians with sufficient knowledge about emicizumab and sufficient knowledge and experience in treatment of hemophilia. Major requirements are described below. Up to 100 medical institutions are estimated to meet the requirements for medical institutions.
  - Requirements for medical institutions:

    Initiating medical institutions where treatment with emicizumab is initiated should be capable of using rFVIIa products, performing coagulation test necessary for concomitant use with bypassing products, and providing appropriate treatment of thromboembolism and thrombotic microangiopathy. Medical institutions (follow-up clinics) which are engaged in routine practices in concert with the initiating medical institution shall be capable of using rFVIIa products and referring patients to the initiating medical institution when hemostasis is not achieved with an rFVIIa product.
  - Requirements for physicians:

    Physicians who use emicizumab should have knowledge and experience in treatment of hemophilia, more specifically, treatment with bypassing products in patients with hemophilia A with inhibitors. In addition, physicians should have knowledge about emicizumab, being informed of the product and safety measures by medical representatives (MRs).
  - The following distribution control is implemented:

    Before the first delivery of emicizumab, an MR checks if requirements for medical institutions and physicians are met, and explains the product and safety measures; only when it is confirmed that all the requirements are met, the first delivery restriction is released, allowing delivery of the product. In addition, an MR explains the product and safety measures to dispensing pharmacies before the first delivery in the same manner as for medical institutions.
- The following information and cautionary instructions regarding use of bypassing products are included in the package insert:
  - Information on use status of aPCC products in patients who experienced thromboembolic events/thrombotic microangiopathy in clinical studies
  - Periodic treatment with bypassing products should be discontinued before start of emicizumab therapy.
  - If a bypassing product is used during treatment with emicizumab, an rFVIIa product should be used, avoiding aPCC and FVIIa/FX products.
  - The treating physician should provide the patient with the following instructions for use of rFVIIa products in advance: how to determine the necessity of use; dose; precaution that the patient should contact the treating physician if hemostasis is not achieved by one self-injection; and actions the patient should take when they cannot contact the treating physician.
  - If there is no choice but to use aPCC or FVIIa/FX product during treatment with emicizumab, it should be used under supervision of a physician at the initiating medical institution in principle, and the patient's coagulation system should be carefully monitored by laboratory tests that cover blood coagulation-related parameters (prothrombin time [PT], APTT, D-dimer, lactate dehydrogenase, platelets, creatinine, FDP, etc.). If any abnormalities are observed, both emicizumab and aPCC or FVIIa/FX product should be discontinued, and appropriate measures should be taken.

- The actions described above should be taken also during the 6 months after discontinuation of emicizumab, because there is a time lag between discontinuation of emicizumab and elimination of the drug from the body. Patients should always carry the "Patient card." When a patient is taken, for emergency or other care, to a medical institution other than the initiating medical institution and follow-up clinic, this card should be presented to healthcare professionals at the medical institution, to inform them that the patient is on emicizumab therapy so that they provide appropriate treatment of bleeding and notify the treating physician at the initiating medical institution about the patient.

PMDA's view:
By the data cut-off date, aPCC products were used in 65 treatment events in 18 subjects during the period of Study BH29884, except for the first 7 days after start of emicizumab and 30 days after discontinuation of emicizumab. Of these, 4 treatment events in 4 subjects were involved in serious thromboembolic events or thrombotic microangiopathy. These events occurred frequently in subjects who received aPCC products concomitantly (4 of 18 subjects [22.2%]). Therefore, use of aPCC products should be avoided during treatment with emicizumab to reduce the risk of thromboembolic events and thrombotic microangiopathy. Such avoidance is critical to ensure the safety of patients.

Conventionally, patients with hemophilia A with inhibitors self-inject bypassing products when mild or moderate bleeding occurs. Use of bypassing products during treatment with emicizumab, however, requires the patients to comply with many instructions to ensure the safety, unlike conventional treatment without emicizumab, and a failure to comply with the instructions may possibly result in a serious outcome. As planned by the applicant, after the market launch, the applicant must inform healthcare professionals and patients about actions they should take in case of bleeding or adverse drug reactions so that they adequately understand the risk of emicizumab before starting the treatment, and must ensure that necessary safety measures are taken.

7.R.4 Indication

Based on results from clinical studies in patients with hemophilia A with inhibitors, PMDA has concluded that the efficacy of periodic treatment with emicizumab can be expected; and thus the proposed indication, "Reduction in bleeding tendency in patients with congenital blood coagulation factor VIII deficiency with blood coagulation factor VIII inhibitors," is acceptable.

PMDA's view on clinical positioning of emicizumab:
aPCC products are approved as bypassing products for periodic treatment in patients with hemophilia A with inhibitors. However, since they are a plasma fraction product, a risk of infectious disease transmission caused by the raw material plasma cannot be completely eliminated. In addition, periodic treatment with aPCC products requires intravenous injection every alternate day.

Emicizumab, on the other hand, is a recombinant drug produced in appropriately controlled CHO cells and no human or animal-derived raw materials are used in its manufacturing process. The drug has therefore lower risk of infectious disease transmission caused by the raw materials. Furthermore, emicizumab is expected to have efficacy with a once-weekly subcutaneous administration. PMDA has

therefore concluded that emicizumab is positioned as a new treatment option for patients with hemophilia A with inhibitors.

7.R.5 Dosage and administration

The dosage used in phase III studies (Studies BH29884 and BH29992), was established based on results from simulations using the population pharmacokinetic model and exposure-response model. In these studies, actually, the plasma emicizumab trough levels in patients aged both ≥12 and <12 years reached ≥45 μg/mL, the target plasma concentration [see Section "6.2 Clinical pharmacology"]. The efficacy and safety of emicizumab at the dosage were confirmed [see Sections "7.R.2 Efficacy" and "7.R.3 Safety"].

In Studies ACE002JP, BH29884, and BH29992, patients injected emicizumab by themselves at home after being trained for self-injection under supervision of a physician at medical institutions. As of now, no efficacy, safety, or procedural issues associated with the self-injection have been reported.

PMDA has concluded that the following dosage and administration of emicizumab is acceptable, irrespective of patient age: "The usual dosage is 3 mg/kg (body weight) of emicizumab (genetical recombination) subcutaneously administered once weekly for 4 doses, followed by 1.5 mg/kg (body weight) subcutaneously administered once weekly." Hemostatic effects during bleeding or surgery have not been investigated in clinical studies, and PMDA considers it appropriate to include a statement in the Precautions Concerning Dosage and Administration section that emicizumab should be used only for periodic treatment. In addition, no particular issues about self-injection have been suggested in clinical studies, and PMDA considers it appropriate to allow patients to do self-injection by providing appropriate cautions and information to them through the package insert, etc.

7.R.6 Post-marketing investigations

The applicant's explanation about post-marketing surveillance for emicizumab:

To investigate the safety and efficacy of emicizumab in clinical use, the applicant plans a use-results survey covering all patients who have received emicizumab (enrollment period, 3 years; observation period, 3 years). Approximately 100 patients are expected to be enrolled in 3 years. This survey will collect information on bleeding episodes and their treatment, thromboembolic events and thrombotic microangiopathy, and other adverse drug reactions.

PMDA's view:

The number of Japanese subjects included in clinical studies of emicizumab is extremely limited, and thus experience with emicizumab in clinical practice in Japan is limited. Accordingly, the applicant should conduct post-marketing surveillance covering all patients receiving emicizumab in clinical practice, to collect information on the safety of emicizumab in clinical use as much as possible. On the basis of the information collected and enrollment status, the applicant should reconsider the surveillance plan and discuss the necessity of collecting further information through the surveillance. Furthermore, the safety information obtained after the market launch should be provided to healthcare professionals in an appropriate and prompt manner, and the post-marketing safety measures described in Section "7.R.3 Safety" should be revised as appropriate.

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

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

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection revealed that the sponsor operated the electronic data processing system inappropriately, so that investigators could not check changes or corrections made to a case report form prepared in the system by investigators etc. Despite of this finding requiring correction, the final data described in case report forms were inspected and confirmed by investigators. PMDA thus concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

The new drug application data (CTD 5.3.3.1-1, CTD 5.3.4.1-1, CTD 5.3.3.2-1, CTD 5.3.4.2-1, CTD 5.3.5.1-1, and CTD 5.3.5.2-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection, PMDA thus concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

On the basis of the data submitted, PMDA has concluded that emicizumab has efficacy in reducing bleeding tendency in patients with congenital FVIII deficiency with FVIII inhibitors. For the safety, because concomitant use of emicizumab with bypassing products may lead to serious thromboembolic events and thrombotic microangiopathy, PMDA considers it essential to ensure that post-marketing safety measures are thoroughly taken for use of emicizumab. Emicizumab is recombinant bispecific monoclonal antibody intended to be substituted for cofactor function of FVIII, and is clinically meaningful because it offers a new treatment option for patients with congenital FVIII deficiency with FVIII inhibitors.

PMDA has concluded that emicizumab may be approved if emicizumab is not considered to have any particular problems with the efficacy, safety, and post-marketing safety measures based on comments from the Expert Discussion.

Review Report (2)

February 9, 2018

Product Submitted for Approval

Brand Name	Hemlibra s.c. 30 mg
	Hemlibra s.c. 60 mg
	Hemlibra s.c. 90 mg
	Hemlibra s.c. 105 mg
	Hemlibra s.c. 150 mg
Non-proprietary Name	Emicizumab (Genetical Recombination)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	July 21, 2017

List of Abbreviations
See Appendix.

1. Content of the Review

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

The expert advisors at the Expert Discussion supported the PMDA's conclusion on issues presented in the Review Report (1) [Sections "7.R.2 Efficacy," "7.R.3 Safety," "7.R.4 Indication," and "7.R.5 Dosage and administration"].

1.1 Risk management plan (draft)

The conclusion of PMDA presented in Section "7.R.6 Post-marketing investigations" of the Review Report (1) was supported by the expert advisors at the Expert Discussion.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for emicizumab should include the safety and efficacy specifications presented in Table 23, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 24 and Table 25.

Table 23. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Thromboembolism (in patients using concomitant aPCC) • Thrombotic microangiopathy (in patients using concomitant aPCC)	• Thromboembolism (in patients using concomitant FVIIa/FX) • Thrombotic microangiopathy (in patients using concomitant FVIIa/FX) • Significant bleeding associated with inappropriate hemostasis control due to impacts of emicizumab on blood coagulation test results • Shock and anaphylaxis • Immunogenicity	None
Efficacy specification		
• Reduction in bleeding by long-term treatment with emicizumab (to be investigated in patients with hemophilia A with inhibitors in Study ACE002JP)		

Table 24. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Post-marketing clinical study[a] • Use-results survey	• Provision of information gathered during the early post-marketing phase vigilance • Establishment of conditions for use (requirements for medical institutions, requirements for physicians, check for conformity to the requirements, distribution control that allows the delivery of emicizumab only to medical institutions informed about the drug in advance by MRs) • Provision of information to healthcare professionals (preparation and provision of guidance for proper use) • Provision of information to patients (preparation and provision of patient handbook and patient card)

a Of patients included in clinical studies supposed to be ongoing even after acquisition of approval (Studies ACE002JP, BH29884, and BH29992), patients who continue treatment with emicizumab for the approved indication at the approved dosage and administration are deemed as patients included in a post-marketing clinical study.

Table 25. Outline of use-results survey (draft)

Objective	To collect bleeding episodes and their treatment, thromboembolic events and thrombotic microangiopathy, and other adverse reactions to emicizumab in clinical practice
Survey method	All-case surveillance
Population	All patients treated with emicizumab
Observation period	3 years
Planned sample size	All patients treated with emicizumab
Main survey items	• Bleeding episodes and their treatment, ABR, and use of emicizumab and bypassing products for hemostasis (type, timing of treatment, and dose) • Thromboembolism and thrombotic microangiopathy: Time of onset, outcome, treatment, use of emicizumab and bypassing products for hemostasis (type, timing of treatment, and dose of the bypassing product for hemostasis) • Other adverse drug reactions: Percentage of patients with adverse drug reactions and their seriousness

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and the dosage and administration shown below, with the following conditions. Because the product is classified as an orphan drug, the re-examination period is 10 years. The product is classified as a biological product, but neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Indication

Reduction in bleeding tendency in patients with congenital blood coagulation factor VIII deficiency with blood coagulation factor VIII inhibitors

Dosage and Administration

The usual dosage is 3 mg/kg (body weight) of emicizumab (genetical recombination) subcutaneously administered once weekly for 4 doses, followed by 1.5 mg/kg (body weight) subcutaneously administered once weekly.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since only a limited number of Japanese patients have received the product, the applicant is required to conduct a drug use-results survey involving all Japanese patients treated with the product after the market launch until data from a certain number of patients have been gathered, in order to understand the characteristics of patients using the product, and to promptly collect safety and efficacy data so that necessary measures are taken to ensure proper use of the product.

Appendix

List of Abbreviations

ABR	Annualized bleeding rate
ADA	Anti-drug antibody
[redacted]	[redacted]
aPCC	Activated prothrombin complex concentrate
APTT	Activated partial thromboplastin time
AUC_{inf}	Area under the plasma concentration-time curve from time zero to extrapolated infinity
AUC_{last}	area under the plasma concentration-time curve from 0 to the last measurable plasma concentration
BU	Bethesda unit
C_0	The initial concentration at time 0 calculated by extrapolation
CAL	Cells at the limit of *in vitro* cell age used for production
CDR	Complementarity-determining region
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
CHO cells	Chinese hamster ovary cells
CL	Clearance
CL/F	Apparent total clearance
C_{max}	Maximum plasma concentration
CQA	Critical quality attribute
CRP	C-reactive protein
ELISA	Enzyme-linked immunosorbent assay
FDP	Fibrin and fibrinogen degradation products
FIX	Factor IX
FIXa	Activated factor IX
FVIIa	Activated factor VII
FVIIa/FX product	Activated blood coagulation factor VIIa concentrate containing factor X
FVIII	Factor VIII
FX	Factor X
FXa	Activated factor X
[redacted]	[redacted]
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IgG	Immunoglobulin G
ITT	Intent-to-treat population
MCB	Master cell bank
MMV	Mouse minute virus
MR	Medical representative
PMDA	Pharmaceuticals and Medical Devices Agency
Poloxamer 188	Polyoxyethylene (160) polyoxypropylene (30) glycol
PT	Prothrombin time
QbD	Quality by design
rFVIIa	Recombinant activated factor VII
SEC	Size-exclusion chromatography
SPR	Surface plasmon resonance
$t_{1/2}$	Elimination half-life
T_{max}	Time to reach maximum plasma concentration
V_d/F	Apparent volume of distribution (estimated by a model-independent analysis)
V_{ss}	Volume of distribution at steady-state
WCB	Working cell bank