Report on the Deliberation Results

June 1, 2018

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

Brand Name	Refixia I.V. Injection 500 Refixia I.V. Injection 1000 Refixia I.V. Injection 2000
Non-proprietary Name	Nonacog Beta Pegol (Genetical Recombination)
Applicant	Novo Nordisk Pharma Ltd.
Date of Application	July 11, 2017

Results of the Deliberation

In its meeting held on May 23, 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, and the reexamination period of this product is 8 years. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Conditions for Approval

The applicant is required to develop and appropriately implement a risk management plan.

Review Report

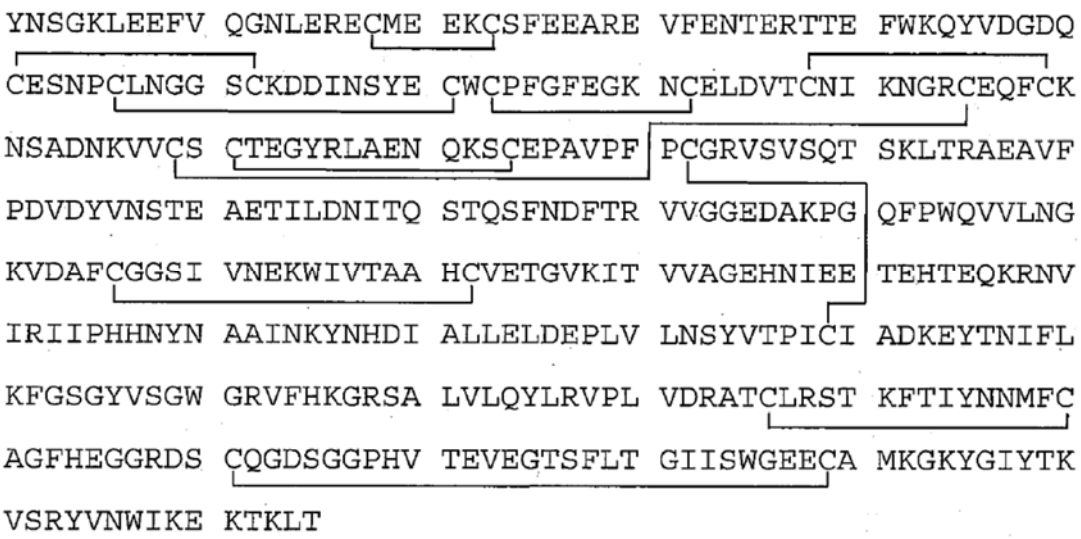
April 27, 2018
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Refixia I.V. Injection 500 Refixia I.V. Injection 1000 Refixia I.V. Injection 2000
Non-proprietary Name	Nonacog Beta Pegol (Genetical Recombination)
Applicant	Novo Nordisk Pharma Ltd.
Date of Application	July 11, 2017
Dosage Form/Strength	Power for solution for injection that requires reconstitution before use. Each vial contains 500, 1000, or 2000 IU of nonacog beta pegol (genetical recombination).
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Definition	Nonacog Beta Pegol is a recombinant human blood coagulation factor IX analogue (molecular weight: ca. 98,000) in which an average of one non-reducing end of a glycan at Asn157 or Asn167 is attached to neuraminic acid conjugated to two polyethylene glycol polymers (total average molecular weight of the polymers: ca. 42,000) via the amino group. The glycoprotein moiety containing 415 amino acid residues is produced in Chinese hamster ovary cells.

Structure

Amino acid sequence and disulfide bond:



N157, N167: glycosylation and PEGylation sites

S53, S61, T159, T163, T169: glycosylation sites

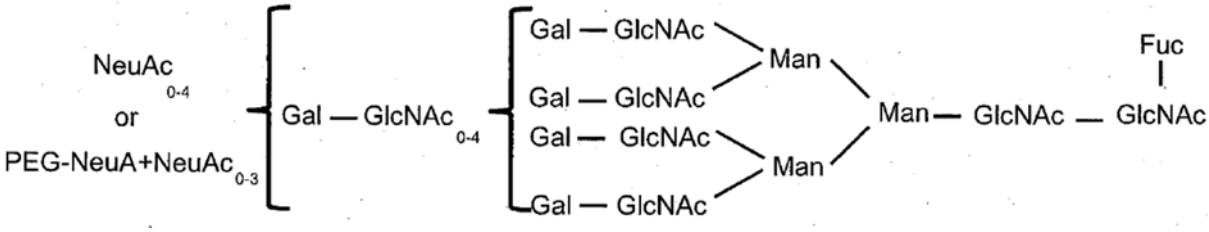
E7, E8, E15, E17, E20, E21, E26, E27, E30, E33*, E36*, E40*: γ-carboxyglutamic acid (*: partially)

Y155: partial sulfation

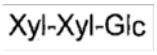
D64: partial beta-hydroxylation

Putative primary carbohydrate structure:

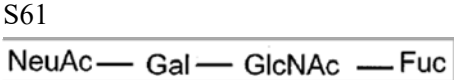
N157, N167



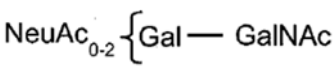
S53



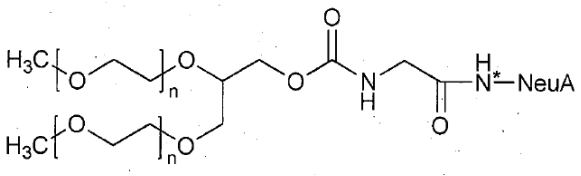
S61



T159, T163, T169 (partially glycosylated)



PEG binding:



*Amino group of NeuA

Molecular formula: $C_{2041}H_{3114}N_{558}O_{641}S_{25}$ (protein part)
Molecular weight: approximately 98,000

Items Warranting Special Mention	None
Reviewing Office	Office of Vaccines and Blood Products

Results of Review

On the basis of the data submitted, PMDA concluded that the product has efficacy in the control of bleeding tendency in patients with factor IX deficiency 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. The safety and efficacy of the product in clinical practice should be further evaluated in post-marketing clinical studies and post-marketing surveillance.

Indication(s)

Control of bleeding tendency in patients with factor IX deficiency

Dosage and Administration

Refixia is administered intravenously after reconstitution of the powder with the whole amount of the attached solvent. Inject the reconstituted solution slowly at a rate of ≤4 mL/min. See dosing guidelines in the table below.

		Dosage and Administration
Treatment of bleeding episodes	Mild to moderate	A dose of 40 IU/kg is recommended. Additional doses of 40 IU/kg can be given, depending on the patient's condition.
	Severe or life threatening hemorrhages	A dose of 80 IU/kg is recommended.
Treatment in surgery	Minor surgery	A pre-operative dose of 40 IU/kg is recommended.
	Major surgery	A pre-operative dose of 80 IU/kg is recommended. If needed, the dose may be adjusted to maintain the blood FIX activity level at approximately 100% (1 IU/mL) during surgery. A post-operative dose of 40 IU/kg is administered 24 to 48 hours after the pre-operative dose, depending on the desired blood FIX activity level. Repeated doses of 40 IU/kg may be given within the first 7 days after surgery to maintain the blood FIX activity level at approximately 50% (0.5 IU/mL).
Routine prophylaxis		A dose of 40 IU/kg once weekly is recommended.

Conditions for Approval

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review report (1)

March 12, 2018

The following is an outline of the data submitted by the applicant and the contents of the review conducted by PMDA.

Product Submitted for Approval

Brand Name	Refixia I.V. Injection 500 Refixia I.V. Injection 1000 Refixia I.V. Injection 2000
Non-proprietary Name	Nonacog Beta Pegol (Genetical Recombination)
Applicant	Novo Nordisk Pharma Ltd.
Date of Application	July 11, 2017
Dosage Form/Strength	Powder for solution for injection that requires reconstitution before use. Each vial contains 500, 1000, or 2000 IU of nonacog beta pegol (genetical recombination) per vial.

Proposed Indication

Control of bleeding tendency in patients with factor IX deficiency

Proposed Dosage and Administration

Refixia is administered intravenously after reconstitution of the powder with the whole amount of the attached solvent. Inject the reconstituted solution slowly at a rate of ≤4 mL/min, depending on the patient's condition.
For routine prophylaxis, the usual adult and pediatric dosage is 40 IU/kg body weight once weekly.
For treatment of bleeding episodes, the usual dosage is 40 IU/kg body weight per dose.
For treatment in major surgery, a pre-operative dose of 80 IU/kg body weight is recommended. If needed, up to two repeated doses of 40 IU/kg body weight within the first 7 days after surgery may be given in 1- to 3-day intervals. Thereafter, additional doses of 40 IU/kg body weight may be given once weekly until hemostasis or healing is achieved.
For control of bleeding in minor surgery (including tooth extraction), a pre-operative dose of 40 IU/kg body weight is recommended. Additional dose(s) may be given, if needed.

Table of Contents

List of Abbreviations

See Appendix.

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

Hemophilia B (congenital factor IX deficiency) is a bleeding disorder caused by reduced or defective factor IX (FIX) and may lead to serious bleeding. Standard of care for patients with hemophilia B is the administration of adequate FIX replacement therapy for hemostasis.

Currently, several human plasma-derived FIX products and recombinant FIX products have been approved in Japan. Nonacog beta pegol was developed as a recombinant human FIX (rFIX) with a PEG molecule (average molecular weight of approximately 42,000) attached to N-linked glycans in the FIX activation peptide. The addition of the PEG moiety to the rFIX is intended to contribute to its prolonged elimination half-life and reduced dosing frequency.

The clinical development program for nonacog beta pegol was undertaken for the treatment of severe hemophilia B, and a global phase III study (Study 3747) was conducted in 15 countries including Japan. An application for marketing approval was submitted based on the results of the clinical study and other studies. As of March 2018, nonacog beta pegol has been approved in 4 countries and regions, including Europe and the United States.

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

2.1 Drug substance

2.1.1 Generation and control of cell substrate

The factor IX gene from human liver mRNA was inserted into an expression vector by using genetic recombination techniques. The obtained gene expression construct was introduced into Chinese hamster ovary (CHO) cells, and an optimal clone was isolated. This cell line was used to create a research cell bank (RCB), master cell bank (MCB), and working cell bank (WCB) in a sequential manner.

Characterization and purity test were performed for the MCB, WCB, and cells at the limit of *in vitro* cell age (CAL) used for production in accordance with the Q5A (R1), Q5B, and Q5D guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).The genetic stability of the cell bank system and the genetic stability during manufacture were confirmed. The tests conducted detected neither viral nor non-viral adventitious agents, except for endogenous retrovirus-like particles that are known to exist in rodent cell lines.

Appropriate storage conditions have been established for the MCB and WCB. Although a new WCB will be established as necessary, there is no plan for generating a new MCB.

2.1.2 Manufacturing process

The manufacturing process of the drug substance consists of the following steps: flask culture, expanded culture using a bioreactor, cell culture in the [redacted] bioreactor, anti-FIX antibody affinity chromatography (AC), Chromatography 1, Chromatography 2, [redacted], Chromatography 3, virus filtration, [redacted],

PEGylation, Chromatography 4, [redacted], Chromatography 5, Chromatography 6, and [redacted]. Cell culture in the [redacted] bioreactor, [redacted], Chromatography 1, Chromatography 2, virus filtration, [redacted], Chromatography 4, Chromatography 5, Chromatography 6, and [redacted] are identified as critical steps. [redacted] are controlled as critical intermediates of the drug substance.

The process validation of the manufacturing process of the drug substance was performed on a commercial production scale.

2.1.3 Safety evaluation of adventitious agents

In the manufacturing process of the drug substance, CHO cells are used as the host cells. Furthermore, the anti-FIX monoclonal antibody generated from CHO cells is used in the anti-FIX antibody AC step. Both ingredients have been confirmed to meet the Standards for Biological Ingredients.

Purity test has been for the MCB, WCB, and CAL [see Section 2.1.1].

An adventitious virus test (*in vitro*) and a mycoplasma test were performed for the cell culture media used in the [redacted] bioreactor. The test detected neither viral nor non-viral adventitious agents.

Viral clearance studies using the model viruses (Table 1) were performed for the manufacturing process, and the results showed a certain level of viral clearance capacity of the purification step. The lowest values obtained from multiple independent tests (including [redacted] in the chromatography step) were employed for the reduction factors in each step.

Table 1. Results of viral clearance studies

Manufacturing process	Virus reduction factor (log_{10})			
	eMuLV	MVM	IBRV	BEV
Anti-FIX antibody AC and [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chromatography 1	[redacted]	[redacted]	[redacted]	[redacted]
Chromatography 2	[redacted]	[redacted]	[redacted]	[redacted]
Virus filtration	[redacted]	[redacted]	[redacted]	[redacted]
Chromatography 5	[redacted]	[redacted]	[redacted]	[redacted]
Overall reduction factor	>18.1	>15.6	>13.6	>12.4

2.1.4 Manufacturing process development (comparability)

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

- Process A → Process B: [redacted], [redacted], [redacted]
- Process B → Process C: Change in [redacted], change in [redacted].
- Process C → Process D: Change in [redacted], change in [redacted], change in [redacted]

[redacted], change in [redacted], and change in [redacted].

- Process D → Process E (the proposed commercial process): Changes in [redacted] and [redacted].
- Process E → Process F (the proposed commercial process): Change in [redacted].

The drug product used in the non-clinical studies was manufactured using the drug substance produced by Processes A and D. The drug product used in the phase I study was manufactured using the drug substance produced by Process B. The drug product used in the phase III study was manufactured using the drug substance produced by Processes D, E, and F [see Sections 3, 4, 5, 7.1, and 7.2]. The quality attributes of the pre-change and post-change drug substances were demonstrated to be comparable.

2.1.5 Characterization

2.1.5.1 Structure and physicochemical and biological properties

Nonacog beta pegol and [redacted] intermediates were characterized (Table 2).

Table 2. Summary of characterization

Properties	
Structure	Primary structure, disulfide bond, glycosylation (N-linked glycans, O-linked glycans, [redacted]), amino acid modifications (γ-carboxylation, [redacted], and [redacted]), PEG and linker structures, secondary structure, and high-order structure
Physicochemical properties	Molecular weight, absorption coefficient, PEGylation profiles, charge variant, solubility, and thermal stability
Biological properties	Specific activity, thrombinogenesis ability, activation by activated coagulation factor XI

2.1.5.2 Product-related substances/Product-related impurities

On the basis of the characterization results, Impurity 1, Impurity 2, Impurity 3, Impurity 4, Impurity 5, and Impurity 6 were identified as product-related impurities. Impurity 1 has been controlled as a critical intermediate. Impurity 2, Impurity 3, Impurity 4, and Impurity 6 have been controlled by the specifications for the drug substance and drug product. Impurity 5 has been demonstrated to be thoroughly removed during the manufacturing process.

No product-related substances have been detected.

2.1.5.3 Process-related impurities

The following substances were identified as process-related impurities: host cell protein (HCP), Impurity 7, host cell-derived DNA, Impurity 8 (Impurity 8-1, Impurity 8-2, and Impurity 8-3), Impurity 9, Impurity 10, Impurity 11, Impurity 12, Impurity 13 (Impurity 13-1 and Impurity 13-2), Impurity 14 (Impurity 14-1 and Impurity 14-2), Impurity 15, and Impurity 16 (Impurity 16-1 and Impurity 16-2). All of these process-related impurities have been demonstrated to be thoroughly removed during the manufacturing process. HCP, Impurity 7, and Impurity 10 have been controlled as critical intermediates. Impurity 11 has been controlled by the specifications for the drug substance.

2.1.6 Control of drug substance

The drug substance specifications consist of content, description, identification (peptide mapping, [redacted]), [redacted], purity test ([redacted]/total impurity/Impurity 2-1/Impurity 3 [redacted], Impurity 4 [redacted], Impurity 2-2 [redacted], Impurity 6 [redacted], [redacted] [redacted], Impurity 11 [redacted]), endotoxins, microbial limits, assay (protein content [redacted], and specific activity [redacted]).

2.1.7 Stability of drug substance

Table 3 shows the primary stability studies of the drug substance.

Table 3. Summary of the primary stability studies of the drug substance

	No. of batches	Storage conditions	Duration of study	Storage form
Long-term testing	3	–80°C ± 10°C	24 months (ongoing)	[redacted] container
Accelerated testing	3	–20°C ± 5°C	6 months	
Stress testing (light)	1	An overall illumination of ≥1,200,000 lux·h and an integrated near-ultraviolet energy of ≥200 W·h/m^2	38 hours	Polypropylene container
Stress testing (temperature)	1	37°C	2 weeks	

Under the long-term test conditions, no particular time-course changes were observed throughout the study period, and the drug substance met the specifications. Under the accelerated test condition, the amount of Impurity 3 was slightly increased. Under the stress test (temperature) conditions, a decrease in [redacted] and increases in Impurity 2, Impurity 3, and Impurity 4 were observed. The stress test (light) showed that the drug substance was photolabile.

On the basis of the above results, a shelf-life of 24 months has been proposed for the drug substance when stored in a [redacted] container at –80°C ± 10°C.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a lyophilized powder for solution for injection containing 500, 1000, or 2000 IU of the active ingredient per vial (with a volume of 12 mL). The excipients contained in the drug product are sodium chloride, L-histidine, purified sucrose, D-mannitol, polysorbate 80, sodium hydroxide, and hydrochloric acid.

The attached solvent for reconstitution is 4.2 mL of L-histidine solution filled in a glass syringe (with a volume of 5 mL). The drug product is classified as a combination product.

2.2.2 Manufacturing process

The manufacturing process of the drug product consists of the preparation and pH adjustment of the buffer, mixing with the drug substance, mixing with water for injection and pH adjustment, filtered sterilization under

[redacted] airflow, vial filling, lyophilization, closure, and cap sealing. [redacted], [redacted], [redacted], [redacted], and [redacted] were identified as the critical steps.

The manufacturing process of the attached solvent consists of mixing, bioburden reduction filtration, [redacted] filtration, filling, and final sterilization. [redacted] was identified as the critical step.

The process validation for each step of the manufacturing process was performed on a commercial production scale.

2.2.3 Manufacturing process development

Major changes made to the manufacturing process during the development of the drug product are as follows:

- Process A → Process B: [redacted]
- Process B → Process C: change in [redacted]
- Process D →Process E (the proposed commercial process): changes in [redacted], [redacted], [redacted], and [redacted]

The drug product used in the non-clinical studies was manufactured by Processes A and B. The drug product used in the phase I study was manufactured by Process A. The drug product used in the phase III study was manufactured by Processes B, C, and D [see Sections 3, 4, 5, 7.1, and 7.2] The quality attributes of the pre-change and post-change drug products were demonstrated to be comparable.

2.2.4 Control of drug product

The drug product specifications consist of strength, appearance, identification ([redacted]), osmotic pressure, pH, dissolution time, purity test ([redacted]/total impurity/Impurity 2-1/Impurity 3 [redacted], Impurity 4 [redacted], Impurity 2-2 [redacted], Impurity 6 [redacted]), water content, endotoxins, insoluble foreign matters, insoluble particles, sterility, protein content ([redacted]), and assay (titer [one-stage clotting assay]).

2.2.5 Stability of drug product

The drug product is supplied in strengths of 500, 1000, or 2000 IU per vial. The composition is the same for the three strengths except for the content of the active ingredient. For the present application, the stability studies were conducted in the bracketing design by using 500 and 2000 IU drug products produced on a commercial production scale as samples on the extremes.

Table 4 summarizes the primary stability studies of the drug product.

Table 4. Summary of the primary stability studies of the drug product

	No. of batches	Storage conditions	Duration of test	Storage form
Long-term testing	500 IU: 3 batches 2000 IU: 3 batches	5°C ± 3°C	24 months (ongoing)	Chlorobutyl rubber stopper and glass vial
Accelerated testing	500 IU: 3 batches 2000 IU: 3 batches	40°C ± 2°C, 75% ± 5% RH	6 months	
Post-reconstitution stability testing	500 IU: 2 batches 2000 IU: 2 batches	5°C ± 3°C	3 to 18 months at 5°C ± 3°C and subsequently 48 hours after reconstitution	
		30°C ± 2°C	3 to 18 months at 5°C ± 3°C and subsequently 24 hours after reconstitution	
Photostability testing	500 IU: 1 batch 2000 IU: 1 batch	11.2°C-22.8°C	An overall illumination of ≥1,200,000 lux・h and an integrated near-ultraviolet energy of ≥200 W・h/m^2	Chlorobutyl rubber stopper and glass vial (with or without a carton)

Under the long-term test conditions, no particular time-course changes were observed throughout the study period, and the drug product met the specifications. Under the accelerated test conditions, a decrease in titer, an increases in [redacted], an increase in Impurity 3, and an increase in impurity were observed. The photostability test showed that the drug product was photolabile. The post-reconstitution stability of the drug product was tested after reconstitution with the attached solvent, and the result showed that the drug product was stable for 48 hours at 5°C ± 3°C and for 24 hours at 30°C ± 2°C.

On the basis of the above findings, a shelf-life of 24 months has been proposed for the drug product when stored in a glass vial plus a carton at 5°C ± 3°C, protected from light or freezing temperature. After reconstitution, the drug product should be used within 24 hours under storage at 5°C ± 3°C or within 4 hours at room temperature.

2.R Outline of the review conducted by PMDA

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

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

3.1 Primary pharmacodynamics

3.1.1 *In vitro* study

3.1.1.1 Activation by FXIa and tissue factor/activated coagulation factor VII complex (CTD 4.2.1.1)

Either activated coagulation factor XI (FXIa) or a complex of tissue factor (TF) and activated coagulation factor VII (FVIIa) (hereinafter "TF-FVIIa") was added to nonacog beta pegol and BeneFIX. Each of the mixtures was analyzed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and coomassie blue staining. After addition of FXIa or TF-FVIIa complex, a band with a molecular size which was expected to represent activated coagulation factor IX (FIXa) was observed for nonacog beta pegol as well as BeneFIX.

3.1.1.2 Activation by FXIa and TF-FVIIa complex and function of FIXa (CTD 4.2.1.1)

Each of nonacog beta pegol, recombinant FIX produced as an intermediate for nonacog beta pegol (N9) (an intermediate of nonacog beta pegol before PEGylation), and BeneFIX was reacted with either FXIa or TF-FVIIa complex to measure FIXa activity. Parameters related to the reaction rate were calculated using the Michaelis-Menten equation. No clear differences in catalytic efficiency (k_{cat}/K_m) were observed among nonacog beta pegol, N9, and BeneFIX after activation by FIXa. By contrast, after activation by TF-FVIIa complex, the catalytic efficiency of nonacog beta pegol was 45% to 50% of those of N9 and BeneFIX. Taking into account the *in vivo* study results described below, the applicant considers that this finding do not affect the hemostatic effect of nonacog beta pegol.

Furthermore, each complex of activated coagulation factor VIII (FVIIIa) and activated nonacog beta pegol, N9, or BeneFIX (tenase [FIXa-FVIIIa] complex) was reacted with coagulation factor X (FX). The activated coagulation factor X (FXa) activity was measured, and parameters related to the reaction rate were calculated using the Michaelis-Menten equation. No clear difference in the reaction rate was observed among nonacog beta pegol, N9, and BeneFIX.

3.1.1.3 Effects on thromboelastography (CTD 4.2.1.1)

Nonacog beta pegol was added to the blood collected from 8 patients with hemophilia B, and the specimens were assessed by thromboelastography (TEG). The result showed that the addition of a higher amount of nonacog beta pegol leads to increased activation of blood coagulation ability (shorter time to initial clot formation and higher maximum clot formation velocity).

3.1.1.4 Effects on thrombin generation (CTD 4.2.1.1)

Either nonacog beta pegol or N9 was added to FIX-deficient plasma derived from patients with hemophilia B, and activation by FXIa or TF was assessed by thrombin generation assay (TGA). For activation by FXIa, the addition of a higher amount of nonacog beta pegol or N9 leads to an increase in maximum thrombin generation and a shorter time to maximum thrombin generation. For activation by TF, the addition of a higher amount of nonacog beta pegol or N9 leads to an increase in maximum thrombin generation, but the time to maximum thrombin generation was not shortened. Furthermore, nonacog beta pegol increased maximum thrombin generation compared with N9. The applicant considers that these findings are consistent with the activation kinetics of nonacog beta pegol [see Section 3.1.1.2].

3.1.2 *In vivo* study

3.1.2.1 Hemostatic effect in FIX knock-out mice using a tail-cut bleeding model (dose response) (CTD 4.2.1.1)

Nonacog beta pegol or BeneFIX at a dose of 0.01, 0.1, 0.2, 0.4, or 0.75 mg/kg, or vehicle (negative control) was administered to FIX knock-out (FIX-KO) mice (a total of 6 to 14 male and female mice per group). At 5 minutes post-dose, the tail was amputated, and then the bleeding time and blood loss (as the hemoglobin level) were measured for 30 minutes. The result showed shorter bleeding time and smaller blood loss in the higher

dose groups of both nonacog beta pegol and BeneFIX (Table 5). On the basis of these findings, the applicant considered that there were no differences in the dose response between nonacog beta pegol and BeneFIX when their hemostatic effects were compared.

Table 5. Hemostatic effect in FIX-KO mice (mean ± SD)

	Vehicle	Nonacog beta pegol (mg/kg)					BeneFIX (mg/kg)				
		0.01	0.1	0.2	0.4	0.75	0.01	0.1	0.2	0.4	0.75
Bleeding time (min)	27.7 ± 3.1	26.5 ± 4.0	17.4 ± 11.2	16.4 ± 11.9	5.3 ± 7.7	3.2 ± 1.4	26.6 ± 5.9	15.5 ± 9.1	13.7 ± 11.4	6.0 ± 6.8	9.3 ± 10.7
Blood loss (nmol)	3374 ± 1145	2741 ± 1988	1406 ± 1517	2679 ± 2738	568.1 ± 814.5	502.6 ± 642.1	4613 ± 1933	2203 ± 2005	1327 ± 1076	698.1 ± 408.7	933.9 ± 1092

3.1.2.2 Hemostatic effect in a tail bleeding model in FIX-KO mice (persistence) (CTD 4.2.1.1)

Nonacog beta pegol or BeneFIX (at a dose of 0.75 mg/kg) was administered to FIX-KO mice (a total of 8 to 16 male and female mice per group). At 5 minutes post-dose or at 1, 2, 3, or 5 days post-dose, the bleeding time and blood loss (as the hemoglobin level) were measured for 30 minutes after tail amputation. Vehicle (negative control) was also administered to FIX-KO mice (for a total of 14 male and female mice). At 5 minutes post-dose, the bleeding time and blood loss (as the hemoglobin level) were measured for 30 minutes after tail amputation. On the basis of the results (Table 6), the applicant considered that the hemostatic effect of nonacog beta pegol persisted longer than that of BeneFIX.

Table 6. Hemostatic effect in FIX-KO mice (mean ± SD)

	Vehicle	Nonacog beta pegol (0.75 mg/kg)					BeneFIX (0.75 mg/kg)				
Time from administration to tail ampulation	5 minutes	5 minutes	1 day	2 days	3 days	5 days	5 minutes	1 day	2 days	3 days	5 days
Bleeding time (min)	27.7 ± 3.1	6.2 ± 6.8	7.6 ± 9.7	6.4 ± 10.1	13.0 ± 11.5	23.7 ± 11.3	9.3 ± 10.7	14.0 ± 11.7	24.4 ± 5.6	24.8 ± 4.9	26.9 ± 3.8
Blood loss (nmol)	3341 ± 1399	911.9 ± 919.3	885.0 ± 1146	461.5 ± 969.8	1501 ± 1610	2858 ± 1729	933.9 ± 1092	1318 ± 1662	2542 ± 1741	3219 ± 1326	3481 ± 1771

3.1.2.3 Hemostatic effect in a ferric chloride-induced injury model in FIX-KO mice (CTD 4.2.1.1)

Nonacog beta pegol or BeneFIX (at a dose of 0.75 mg/kg) was administered to FIX-KO mice (a total of 6 to 11 male and female mice per group). At 5 minutes post-dose or at 1, 2, 3, 4, or 5 days post-dose, the injury was induced by applying ferric chloride to the carotid artery (*Microcirculation* 2005; 12: 259-74). Subsequently, the time to vascular occlusion was determined (for up to 25 minutes). Vehicle (negative control) was also administered to FIX-KO mice (a total of 6 male and female mice). At 5 minutes post-dose, the injury was induced by applying ferric chloride to the carotid artery. Subsequently, the time to vascular occlusion was determined (for up to 25 minutes). On the basis of the results (in Table 7), the applicant considered that the hemostatic effect of nonacog beta pegol persisted longer than that of BeneFIX.

Table 7. Persistence of the hemostatic effect in FIX-KO mice (ferric chloride-induced injury model)

	Vehicle	Nonacog beta pegol (0.75 mg/kg)						BeneFIX (0.75 mg/kg)					
Time from administration to vascular injury	5 minutes	5 minutes	1 day	2 days	3 days	4 days	5 days	5 minutes	1 day	2 days	3 days	4 days	5 days
Time to vascular occlusion (min) (mean ± SD)	25 ± 0	8.3 ± 5.1	8.0 ± 6.5	6.5 ± 2.5	6.4 ± 1.9	9.4 ± 5.7	14.7 ± 10.0	7.7 ± 2.1	12.7 ± 8.7	12.0 ± 7.6	14.6 ± 7.1	19.5 ± 6.8	23.0 ± 5.6
Proportion of animals with vascular occlusion (%)	0	100	89	100	100	90	56	100	70	78	73	44	13

3.1.2.4 Hemostatic effect in a knee joint injury model in FIX-KO mice (CTD 4.2.1.1)

Knee-joint bleeds were induced in FIX-KO mice. The mice were given 1 or 2 intravenous (IV) doses of nonacog beta pegol 250 IU/kg between Day 0 and Day 7 (post-injury) or 1, 2, 3, or 8 IV doses of BeneFIX 250 IU/kg between Day 0 and Day 13 (6 to 8 males/group). Normal saline (negative control) was administered to FIX-KO mice on the day of injury (8 males). Histopathological examination was performed to determine the synovitis score (*Haemophilia*. 2006; 12: 654-62) on Day 14, and the result showed a lower score in the nonacog beta pegol group than in the BeneFIX group (Table 8). On the basis of these findings, the applicant considered that the effect of a single dose of nonacog beta pegol was superior to that of an equivalent dose of BeneFIX in terms of a reduction in the aggravation of synovitis. The effect of a single dose of nonacog beta pegol is likely to be comparable to the effect of multiple doses of BeneFIX.

Table 8. Hemostatic effect in FIX-KO mice using a knee joint injury model

	Normal saline	Nonacog beta pegol (250 IU/kg/dose)		BeneFIX (250 IU/kg/dose)			
No. of doses given	1	1	2	1	2	3	8
Timing of administration (no. of days post-injury)	0	0	0 and 7	0	0 and 7	0, 1, and 3	0, 1, 3, 5, 7, 9, 11, and 13
No. of animals	8	7	7	6	7	8	8
Synovitis score (mean ± SE)	5.87 ± 0.20	1.76 ± 0.35	1.71 ± 0.33	3.77 ± 0.55	3.80 ± 0.20	2.45 ± 0.56	2.12 ± 0.30

3.1.2.5 Pharmacodynamic effects in a hemophilia B dog (CTD 4.2.1.1)

Nonacog beta pegol (0.4 mg/kg) was administered to 1 female dog model of hemophilia B with immune tolerance to human FIX (*Prog Mol Biol Transl Sci*. 2012; 105: 151-209) to evaluate the time-course changes in the pharmacodynamic effects (whole blood clotting time [WBCT] and TEG). After the disappearance of the effects of nonacog beta pegol, 0.4 mg/kg of BeneFIX was administered to the animal to evaluate the time-course changes in the pharmacodynamic effects in the same manner. Nonacog beta pegol showed a longer pharmacodynamic effect than BeneFIX.

3.2 Secondary pharmacodynamics

3.2.1 Binding to human umbilical vein endothelial cells (CTD 4.2.1.2)

The specific binding of nonacog beta pegol to vascular endothelial cells, which is a property of FIX, was assessed *in vitro*. Human umbilical vein endothelial (HUVE) cells were incubated with ^{125}I-labeled BeneFIX or non-labeled nonacog beta pegol to assess the binding based on the radiation level. The result showed

competitive binding to HUVE cells between nonacog beta pegol and BeneFIX. This finding demonstrated the specific binding of nonacog beta pegol to vascular endothelium.

3.3 Safety pharmacology

Table 9 shows the effects of nonacog beta pegol on the central nervous, cardiovascular, and respiratory systems, which were assessed in the repeated-dose toxicity studies [see Section 5.2].

Table 9. Summary of safety pharmacology results

System	Test system	Parameter and method of evaluation	Maximum dose	Route of administration	Findings	Location in CTD
Central nervous system	Monkeys (5 to 8 males per group)	Neurological observation	3750 IU/kg/week, 4 doses	IV	Nonacog beta pegol showed no effects on the central nervous system, except for transient systemic tremor observed in the maximum dose group [see Section 5.2].	4.2.3.2
Cardiovascular system		Blood pressure, ECG			Nonacog beta pegol showed no effects on the cardiovascular system.	
Respiratory system		Respiratory rate			Nonacog beta pegol showed no effects on the respiratory system.	

3.R Outline of the review conducted by PMDA

On the basis of the submitted primary pharmacodynamics study data, PMDA concluded that nonacog beta pegol has FIX activity that is expected to contribute to hemostasis *in vivo*. Furthermore, on the basis of the submitted safety pharmacology study data, no particular safety concerns of nonacog beta pegol were identified.

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

Plasma FIX levels were determined by one-stage clotting assay or enzyme-linked immunosorbent assay (ELISA). Following the administration of the ^{3}H-labeled protein part of nonacog beta pegol (^{3}H-labeled nonacog beta pegol), ^{3}H-labeled PEG part of nonacog beta pegol (^{3}H-labeled PEG-nonacog beta pegol) and ^{3}H-labeled PEG, tissue radioactivity was determined using quantitative whole-body autoradiography. Furthermore, following the administration of ^{3}H-labeled PEG-nonacog beta pegol, the ^{14}C-labeled linker part of nonacog beta pegol (^{14}C-labeled linker-nonacog beta pegol) and ^{3}H-labeled PEG, radioactivity in the excreta and carcass was determined using liquid scintillation counting or accelerator mass spectrometry.

4.1 Absorption

4.1.1 Single-dose studies (CTD 4.2.1.1 and CTD 4.2.2.2)

A single IV dose of 1.5 mg/kg of nonacog beta pegol or BeneFIX was administered to FIX-KO mice (3 animals/group/measurement point). Plasma FIX levels were determined for a total of 15 points from 5 minutes to 168 hours post-dose.

A single IV dose of 0.4 mg/kg of nonacog beta pegol or BeneFIX was administered to hemophilia B dogs (1 female/group). Plasma FIX levels were determined for a total of 18 points at pre-dose and 5 minutes to 216 hours post-dose.

A single IV dose of 0.2 mg/kg of nonacog beta pegol or BeneFIX was administered to minipigs (3 male/group). Plasma FIX levels were determined for a total of 20 points at pre-dose and 5 minutes to 28 days post-dose in the nonacog beta pegol group and for a total of 13 points at pre-dose and 5 minutes to 6 days post-dose in the BeneFIX group.

Table 10 shows the pharmacokinetic (PK) parameters. In all of the species tested, the $t_{1/2}$ of nonacog beta pegol was longer than that of BeneFIX.

Table 10. PK parameters assessed in FIX-KO mice, hemophilia B dog, and minipigs[a)]

Species (measurement method)	Test drug	Dose (mg/kg)	No. of animals	C_{max} (ng/mL)	CL (mL/h/kg)	AUC (ng·h/mL)	$t_{1/2}$ (h)
FIX-KO mice (ELISA)	Nonacog beta pegol	1.5	3	15,500	3.6	412,465	41
	BeneFIX	1.5	3	8777	36	41,624	17
Hemophilia B dogs (one-stage clotting assay)	Nonacog beta pegol	0.4	1	6321	0.62	646,594	113
	BeneFIX	0.4	1	3434	13	31,170	18
Minipigs (ELISA)	Nonacog beta pegol	0.2	3	1993 ± 220	1.7 ± 0.2	117,178 ± 16,686	76 ± 3
	BeneFIX	0.2	3	1850 ± 165	12 ± 1	16,991 ± 1328	16 ± 5

a) The parameters in FIX-KO mice were calculated from the mean plasma levels obtained from 3 animals per sampling point. The dog data were obtained from 1 animal. The minipig data were the mean ± standard deviation (SD) obtained from 3 animals.

4.2 Distribution (CTD 4.2.2.3)

In the study using ^{3}H-labeled nonacog beta pegol, a single IV dose of 2.2 mg/kg of ^{3}H-labeled nonacog beta pegol was administered to FIX-KO mice (1 male/sampling time point). Radioactivity was measured for a total of 7 time points between 1 and 336 hours post-dose. In many tissues, the highest radioactivity levels were detected at 1 hour post-dose, and radioactivity levels were high in blood, plasma, liver, kidneys, adrenal gland, and spleen.

In the study using ^{3}H-labeled PEG-nonacog beta pegol, a single IV dose of 2.8 mg/kg of ^{3}H-labeled PEG-nonacog beta pegol was administered to FIX-KO mice (1 male/sampling time point) and a single IV dose of 1.5 mg/kg of ^{3}H-labeled PEG-nonacog beta pegol was administered to rats (1 male/sampling time point). Radioactivity was measured for a total of 9 time points between 1 hour and 12 weeks post-dose. In mice, the highest radioactivity levels were detected during the first 24 hours post-dose in all tissues examined, and radioactivity levels were high in plasma, urinary bladder, blood, liver, adrenal gland, kidneys, and spleen. In rats, radioactivity levels were high in plasma, urinary bladder, blood, bile duct, liver, bulbourethral gland, adrenal gland, and lung during the first 24 hours post-dose.

In the study using ^{3}H-labeled PEG, a single IV dose of 0.6 mg/kg of ^{3}H-labeled PEG was administered to rats (1 male/sampling time point). Radioactivity was measured for a total of 9 time points between 1 hour and 12 weeks post-dose. In many tissues, the highest radioactivity levels were detected at 1 or 12 hours post-dose, and radioactivity levels were high in plasma, urinary bladder, blood, lymph, lungs, bile duct, adrenal gland, and

kidneys.

The applicant's discussion about these findings:
The assessment of radioactivity distribution showed that nonacog beta pegol was distributed mainly to tissues and organs with high blood flow. In the repeated-dose toxicity studies [see Section 5.2], PEG was detected in the brain and choroid plexus, in which a low level of radioactivity was observed. This result was consistent with the findings for other PEGylation products (*Drug Metab Dispos*. 2013;41:774-84, OMONTYS [peginesatide] PHARMACOLOGY REVIEW(S) [https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202799Orig1s000PharmR.pdf, last accessed on March 12, 2018]).

4.3 Metabolism (CTD 4.2.2.4)

The applicant has explained that the protein part of nonacog beta pegol is decomposed to amino acid (i.e. protein decomposition) in the same manner as other protein drug products.

To evaluate the metabolism of the PEG part of nonacog beta pegol, the metabolites in plasma, urine, and feces collected from the following test animals were analyzed by high-performance liquid chromatography (HPLC): FIX-KO mice receiving a single IV dose of 2.8 mg/kg of ^{3}H-labeled PEG-nonacog beta pegol (2 males per sampling time point for plasma and 3 to 4 males per sampling time point for urine and feces), and rats receiving a single IV dose of 1.5 mg/kg of ^{3}H-labeled PEG-nonacog beta pegol or 1 mg/kg of ^{3}H-labeled PEG (6 males per sampling time point for plasma and 3 males per sampling time point for urine and feces). In plasma from mice and rats receiving ^{3}H-labeled PEG-nonacog beta pegol, peaks corresponding to nonacog beta pegol and 40 kDa PEG were detected, and the peak corresponding to nonacog beta pegol decreased over time. In plasma from rats receiving ^{3}H-labeled PEG, a peak corresponding to 40 kDa PEG was detected. In urine and feces from mice and rats receiving any of these test drugs, 40 kDa PEG and PEG with smaller molecular weight were also detected.

On the basis of these findings, the applicant considered that nonacog beta pegol was decomposed to PEG and protein in plasma and that PEG was further decomposed to smaller PEG in the liver, kidney, urine, and feces.

4.4 Excretion (CTD 4.2.2.5)

Following the administration of a single IV dose of radiolabeled nonacog beta pegol (^{3}H-labeled PEG-nonacog beta pegol, ^{14}C-labeled linker-nonacog beta pegol) or ^{3}H-labeled PEG to FIX-KO mice or rats, radioactivity in the excreta and carcass was measured for up to 12 weeks post-dose. Table 11 shows the results. Most of the radioactivity was found to be excreted in urine or feces during the first 12 weeks post-dose.

Table 11. Estimated recovery of radioactivity during the first 12 weeks post-dose (mean ± SD)

Species	Test drug	Dose (mg/kg)	No. of animals	Estimated recovery of radioactivity (%)				
				Urine	Feces	Cage rinse[a)]	Carcasses	Total
FIX-KO mice	^{3}H-labeled PEG-nonacog beta pegol	2.8	4	21 ± 7	50 ± 6	19 ± 5	11 ± 2	103 ± 13
Rats		1.5	3	36 ± 3	28 ± 4	8 ± 1	5 ± 2	77 ± 4
	^{14}C-labeled linker-nonacog beta pegol	0.30	3	49 ± 10	49 ± 4	7 ± 1	7 ± 4	112 ± 12
	^{3}H-labeled PEG	1	3	69 ± 3	13 ± 1	6 ± 3	5 ± 3	93 ± 2
		12	3	68 ± 1	13 ± 2	5 ± 1	6 ± 4	93 ± 3
		100	3	52 ± 4	12 ± 4	3 ± 2	20 ± 1	88 ± 3
		200	3	58 ± 6	12 ± 2	4 ± 1	18 ± 4	93 ± 4

a) The radioactivity in cage rinse was inferred to be derived from urine.

4.R Outline of the review conducted by PMDA

PMDA's view:

The evaluation of PKs of nonacog beta pegol raised no particular concerns. Furthermore, the submitted PK study data indicated that the $t_{1/2}$ of nonacog beta pegol tended to be longer than that of BeneFIX.

5. Toxicity and Outline of the Review Conducted by PMDA

For assessment of the safety of nonacog beta pegol, single-dose and repeated-dose toxicity studies, local tolerance study, and immunogenicity study were performed. The toxicity of PEG was also assessed.

5.1 Single-dose toxicity

Test system	Route of administration	Dose (IU/kg)	Major findings	Approximate lethal dose (IU/kg)	Location in CTD
Male and female rats (Wistar)	IV	0[a)], 200, 1000, 2000	No toxicological changes were observed.	>2000	4.2.3.1

a) Vehicle

5.2 Repeated-dose toxicity

Test system	Route of administration	Duration of dosing	Dose (IU/kg/dose)	Major findings	NOAEL (IU/kg/dose)	Location in CTD
Male and female rats (Rowett nude)	IV	26 weeks (once every 5 days) + 26-week washout period	0[a)], 40, 150, 600, 1200	No toxicological changes were observed. (Although PEG was detected in choroid plexus epithelial cells, no toxicological changes were identified.)	1200	4.2.3.2
Male cynomolgus monkeys	IV	4 weeks (once weekly) + 5-week washout period	0[a)], 350, 1300, 3750	3750: transient systemic tremor (Other findings included changes attributed to xenogeneic immune reaction to rFIX molecules (≥1300) and the presence of PEG in choroid plexus epithelial cells (≥350); however, these were not considered toxicity findings.)	1300	4.2.3.2

a) Vehicle
NOAEL: No-observed-adverse-effect level

5.3 Genotoxicity

Because the components of nonacog beta pegol were considered to be free of genotoxic potential, no genotoxicity study was performed.

5.4 Carcinogenicity

No findings from the previous studies of nonacog beta pegol showed any evidence suggestive of carcinogenic potential for the components. Furthermore, the 26-week repeated-dose toxicity study of nonacog beta pegol in nude rats showed no carcinogenic potential. Therefore, no carcinogenicity study was conducted.

5.5 Reproductive and developmental toxicity

No reproductive and developmental toxicity study was conducted for the following reasons: (i) Thrombogenesis has been known to be one of the risk factors of recurrent pregnancy losses (*Nat Rev Rheumatol*. 2011; 7: 330-9; *Obstet Gynecol.* 2007; 109: 1146-55) and (ii) if a reproductive and developmental toxicity study is conducted in normal animals, long-term exposure to nonacog beta pegol may lead to the development of antibodies, thus precluding toxicity evaluation. No adverse events (AEs) related to reproductive and developmental toxicity have been reported for currently available recombinant coagulation factor IX (rFIX) products. The toxicity study of nonacog beta pegol in rats did not show any findings that may affect the male and female reproductive organs.

5.6 Local tolerance[a)]

Type of study	Test system	Study design	Major findings	Location in CTD
Local tolerance study in rabbits via paravenous, intravenous, and intraarterial administration	Male rabbits (NZW)	Nonacog beta pegol 0.23 mL (500 IU/mL) was administered via the paravenous, intravenous, or intraarterial route. Nonacog beta pegol and vehicle were administered to the right and left ears, respectively.	Mild local reaction was observed in the paravenous and intravenous administration groups, and severe local reaction was observed in the intraarterial administration group. The changes were reversible.	4.2.3.6

a) Local tolerance was assessed in the repeated-dose toxicity studies in rats and monkeys. No particular test article-related changes were observed.

5.7 Other toxicity studies

5.7.1 Immunogenicity in rats

Test system	Route of administration	Duration of dosing	Dose (IU/kg/dose)	Major findings	Location in CTD
Male and female rats (Wistar)	IV	4 cycles of 14-day dosing period (nonacog beta pegol, once weekly; BeneFIX, daily) + a washout period (nonacog beta pegol, 13 days; BeneFIX, 7 days)	Nonacog beta pegol: 25, 200; BeneFIX (comparator): 25, 200	No clear difference was observed in the development of antidrug antibody between nonacog beta pegol and BeneFIX.	4.2.3.7.1

5.7.2 Toxicity of 40 kDa PEG

Test system	Route of administration	Duration of dosing	Dose (mg/kg/week)	Major findings	Location in CTD
Male and female rats (Wistar)	IV	2 or 6 weeks (once every 2 days)	0 (2 and 6 weeks), 45[a)] (2 weeks), 45[a)] (6 weeks), 117 (6 weeks)	Decreased food consumption and body weight (males) Vacuolation of the choroid plexus, spleen, mandibular lymph node, and mesenteric lymph node	Reference 4.2.3.7.7
Male cynomolgus monkeys	IV	2, 6, or 13 weeks (once every 2 days)	45[a)] (2 weeks), 45[a)] (6 weeks), 7 (13 weeks)	45 mg/kg/week for 6weeks: vacuolation of the choroid plexus epithelial cells	Reference 4.2.3.7.7

a) Corresponding approximately to a 196-fold higher PEG dose at the clinical dose of nonacog beta pegol (40 IU/kg/week).

5.R Outline of the review conducted by PMDA

On the basis of the toxicological evaluation results of nonacog beta pegol, PMDA concluded that there were no particular concerns.

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

6.1 Summary of biopharmaceutical studies and associated analytical methods

6.1.1 Measurement method of plasma FIX activity

Plasma FIX activity was measured by one-stage clotting assay.

The clinical pharmacology study of nonacog beta pegol verified that the plasma FIX activity of nonacog beta pegol was properly determined by one-stage clotting assay. An examination of commercially available reagents (activated partial thromboplastin time [aPTT] reagents) revealed that apparent low or high values were obtained by some of aPTT reagents. If these aPTT reagents are used, plasma FIX activity may be under- or overestimated. Therefore, the applicant explained that the following information should be provided in the package insert: Appropriate reagents should be chosen to measure the plasma FIX activity of nonacog beta pegol.

6.2 Clinical pharmacology

The applicant submitted clinical pharmacology evaluation data in the form of results data from a global phase I study (CTD 5.3.3.2.1, Study 3639) and global phase III studies (CTD 5.3.5.2.1, Study 3747; CTD 5.3.5.2.4, Study 3774).

6.2.1 Evaluation in patients

6.2.1.1 Global phase I study (CTD 5.3.3.2.1, Study 3639, Study period from August 2009 to July 2010)

The PK properties of nonacog beta pegol were assessed in 15 patients aged ≥18 and ≤65 years with severe hemophilia B (FIX activity ≤2%), including 3 Japanese patients, with no history of inhibitors, who were previously treated patients with have a history of ≥150 exposure days to other FIX products. The subjects received a single IV dose of the subjects' previously used, currently available FIX products at a dose of 25, 50, or 100 IU/kg (5 subjects per dose), followed by a washout period of ≥7 days, and then received a single IV dose of nonacog beta pegol at the same dose level. The plasma FIX activity was measured for a total of 9 time

points at pre-dose and at 30 minutes to 48 hours post-dose for currently available FIX products and for a total of 13 time points at pre-dose and at 30 minutes to 168 hours post-dose for nonacog beta pegol. Table 12 shows the PK parameters. The applicant explained that the $t_{1/2}$ of nonacog beta pegol was longer than that of currently available FlX products and that the AUC and C_{30min} of nonacog beta pegol were linear over the dose range tested.

Table 12. PK parameters of nonacog beta pegol and currently available FIX products (mean ± SD)

	Nonacog beta pegol			Currently available FIX products		
	25 IU/kg (n = 5)	50 IU/kg (n = 5)	100 IU/kg (n = 5)	25 IU/kg (n = 5)	50 IU/kg (n = 5)	100 IU/kg (n = 5)
$t_{1/2}$ (h)	82.9 ± 18.2	96.3 ± 41.9	110.5 ± 17.5	20.5 ± 6.1	21.2 ± 5.5	15.7 ± 2.5
IR ([IU/mL]/[IU/kg])	0.0140 ± 0.0004	0.0139 ± 0.0044	0.0128 ± 0.0023	0.0075 ± 0.0025	0.0128 ± 0.0043 a)	0.0093 ± 0.0025
AUC (IU·h/mL)	33.0 ± 3.6	73.3 ± 23.1	158.8 ± 37.9	3.5 ± 0.6	9.6 ± 2.9	16.9 ± 2.1
CL (mL/h/kg)	0.8 ± 0.1	0.7 ± 0.2	0.7 ± 0.1	7.3 ± 1.2	5.6 ± 1.6	6.0 ± 0.7
MRT (h)	105.9 ± 16.8	132.7 ± 48.3	151.2 ± 17.7	26.3 ± 7.4	22.8 ± 3.6	20.9 ± 2.0
V_{ss} (mL/kg)	80.2 ± 9.0	94.9 ± 35.6	97.3 ± 11.9	193.1 ± 65.3	129.9 ± 51.0	125.5 ± 24.9
C_{30min} (IU/mL)	0.35 ± 0.01	0.70 ± 0.22	1.28 ± 0.23	0.19 ± 0.06	0.64 ± 0.22 a)	0.93 ± 0.25

a) Excluding the data from 1 subject whose plasma FIX activity at 30 minutes post-dose were unavailable.

Furthermore, Table 13 shows the PK parameters from each of the 3 Japanese subjects (50 IU/kg for 2 subjects, 100 IU/kg for 1 subject). The applicant explained that no Japanese-specific trend was observed in the PK parameters compared with those in the overall population.

Table 13. PK parameters in Japanese subjects

	Nonacog beta pegol			Currently available FIX products		
	Subject 1 (50 IU/kg)	Subject 2 (50 IU/kg)	Subject 3 (100 IU/kg)	Subject 1 (50 IU/kg)	Subject 2 (50 IU/kg)	Subject 3 (100 IU/kg)
$t_{1/2}$ (h)	73.7	154.1	83.4	19.5	17.0	15.5
IR ([IU/mL]/[IU/kg])	0.0158	0.0181	0.0114	0.0169	0.0162	0.0080
AUC (IU·h/mL)	75.6	111.0	126.8	12.2	13.1	16.4
CL (mL/h/kg)	0.7	0.5	0.8	4.1	3.8	6.1
MRT (h)	106.9	206.0	123.7	19.7	19.3	19.8
V_{ss} (mL/kg)	70.7	92.8	97.6	80.8	73.7	120.6
C_{30min} (IU/mL)	0.8	0.9	1.1	0.8	0.8	0.8

6.2.1.2 Global phase III study (CTD 5.3.5.2.1, Study 3747, Study period from April 2011 to April 2013)

The PK properties of nonacog beta pegol were assessed in 16 patients aged ≥13 and ≤70 years with severe hemophilia B (FIX activity ≤2%), including 1 Japanese patient, with no history of inhibitors, who were previously treated patients with a history of ≥150 exposure days to other FIX products. The subjects received repeated IV doses of nonacog beta pegol 10 IU/kg (n = 7) or 40 IU/kg (n = 9) once weekly. The plasma FIX activity was measured after the first dose and at steady state (≥12 weeks of treatment) for a total of 7 time points at pre-dose and at 30 minutes to 168 hours post-dose. Table 14 shows the PK parameters. The applicant explained that the AUC and C_{168h} (corresponding to trough levels after once-weekly administration) were higher in the 40 IU/kg group than in the 10 IU/kg group, regardless of time point (i.e., after the first dose or at steady state). At steady state, no Japanese-specific trend was observed in the PK parameters compared with those in the overall population.

Table 14. PK parameters of nonacog beta pegol after the first dose and at steady state (mean ± SD)

	Overall population				Japanese subjects
	First dose		Steady state		Steady state
	10 IU/kg (n = 4[a])	40 IU/kg (n = 9)	10 IU/kg (n = 7)	40 IU/kg (n = 9)	10 IU/kg (n = 1)
$t_{1/2}$ (h)	93.9 ± 17.3 [b]	86.8 ± 17.4	109.1 ± 23.4 [c]	111.5 ± 13.0	101.4
IR ([IU/mL]/[IU/kg])	0.0252 ± 0.0052	0.0223 ± 0.0032	0.0258 ± 0.0027	0.0192 ± 0.0039	0.0238
AUC (IU·h/mL)	24.1 ± 6.2 [b]	88.7 ± 18.0	44.5 ± 25.7 [c]	143.3 ± 27.0	32.0
CL (mL/h/kg)	0.4 ± 0.1 [b]	0.4 ± 0.1	0.3 ± 0.1 [c]	0.4 ± 0.1	0.4
MRT (h)	127.1 ± 26.1 [b]	120.6 ± 24.1	147.6 ± 32.3 [c]	154.3 ± 17.6	140.7
V_{ss} (mL/kg)	49.5 ± 13.9 [b]	51.2 ± 8.2	48.1 ± 13.7 [c]	64.9 ± 11.7	57.9
C_{168h} (IU/mL)	0.047 ± 0.014 [b]	0.170 ± 0.054 [d]	0.092 ± 0.055 [c]	0.315 ± 0.058 [d]	0.067

a) For 3 subjects who had participated in Study 3639, the PK parameters after the first dose were not evaluated.
b) Excluding the data from 1 subject who was withdrawn from the study after blood sampling at 8 hours post-dose.
c) Excluding the data from 1 subject who discontinued PK assessment due to treatment of bleeding after blood sampling at 24 hours post-dose.
d) Excluding the data from 1 subject whose plasma FIX activity at 168 hours post-dose were unavailable.

6.2.1.3 Global phase III study (CTD 5.3.5.2.4, Study 3774, conducted from May 2012 to April 2014)

The PK properties of nonacog beta pegol were evaluated in 25 patients aged ≤12 years with severe hemophilia B (FIX activity ≤2%), including 3 Japanese patients, with no history of inhibitors, who were previously treated patients with a history of ≥50 exposure days to other FIX products. Following the administration of a single IV dose of nonacog beta pegol 40 IU/kg, the plasma FIX activity was measured for a total of 6 time points at pre-dose and at 30 minutes to 168 hours post-dose. Table 15 shows the PK parameters. The applicant explained that the PK parameters of nonacog beta pegol in subjects aged ≤6 years were almost comparable with those in the subjects aged ≥7 and ≤12 years. Furthermore, incremental recovery (IR) tended to be lower and clearance (CL) tended to be higher in subjects aged ≤12 years in this study than in subjects aged ≥13 and ≤70 years in Study 3747. These trends are similar to that in the reports of currently available FIX products (*Haemophilia*. 2013; 19: 882-6; *Haemophilia*. 2006; 12: 61-9). There were no specific trends in the PK parameters in Japanese subjects compared with those in the overall population.

Table 15. PK parameters of nonacog beta pegol in pediatric subjects (mean ± SD)

	Overall population		Japanese subjects		
	≥0 and ≤6 years of age (n = 12)	≥7 and ≤12 years of age (n = 13)	Subject 1 (5 years of age)	Subject 2 (7 years of age)	Subject 3 (9 years of age)
$t_{1/2}$ (h)	70.3 ± 9.7	78.8 ± 23.6	72.6	81.1	64.2
IR ([IU/mL]/[IU/kg])	0.0152 ± 0.0011 [a]	0.0161 ± 0.0027	0.0141	0.0150	0.0186
AUC (IU·h/mL)	46.6 ± 6.6	57.1 ± 10.4	47.1	51.1	65.1
CL (mL/h/kg)	0.8 ± 0.1	0.7 ± 0.1	0.7	0.7	0.6
MRT (h)	96.3 ± 13.0	108.2 ± 29.9	101.1	113.0	87.9
V_{ss} (mL/kg)	73.0 ± 10.8	69.8 ± 15.3	74.1	76.0	52.3
C_{168h} (IU/mL)	0.085 ± 0.013 [b]	0.110 ± 0.020 [b]	0.092	0.106	0.104

a) Excluding the data from 1 subject whose plasma FIX activity at pre-dose and 30 minutes post-dose were unavailable.
b) Excluding the data from 1 subject whose plasma FIX activity at 168 hours post-dose were unavailable.

6.R Outline of the review conducted by PMDA

PMDA's view:

The results of clinical pharmacology evaluation of nonacog beta pegol showed that there were no particular concerns. The $t_{1/2}$ of nonacog beta pegol was found to be longer than those of currently available FIX products. The appropriateness of treatment regimens for routine prophylaxis is discussed in Section 7.R.2 because it should be examined in consideration of the dosing regimens employed in the clinical studies and efficacy

results.

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

The applicant submitted efficacy and safety evaluation data in the form of results data from the global phase I study (CTD 5.3.3.2.1, Study 3639) and global phase III studies (CTD 5.3.5.2.1, Study 3747; CTD 5.3.5.2.3, Study 3773; CTD 5.3.5.2.7, Study 3775) and in the form of interim analysis results data from the global phase III study (CTD 5.3.5.2.4, Study 3774). Table 16 shows the list of the major clinical studies.

Table 16. List of clinical studies

Region	Study identifier	Phase	Target population	No. of subjects enrolled (no. of Japanese subjects)	Summary of dosing regimen	Primary endpoint
Global	Study 3639	I	Patients with severe hemophilia B (18-65 years of age)	N = 18 (n = 3)	A single dose of the subjects' previous medications (pdFIX or rFIX products) and a single dose of nonacog beta pegol 25, 50, or 100 IU/kg	Safety, PK
Global	Study 3747	III	Patients with severe hemophilia B (13-70 years of age)	N = 74 (1) n = 30 (n = 4) (2) n = 29 (n = 2) (3) n = 15 (n = 2)	(1) Routine prophylaxis (low dose): nonacog beta pegol 10 IU/kg once-weekly (2) Routine prophylaxis (high dose): nonacog beta pegol 40 IU/kg once-weekly (3) On-demand treatment: no routine prophylaxis with nonacog beta pegol For both the routine prophylaxis and on-demand treatment groups: • Mild or moderate bleeds were treated with nonacog beta pegol 40 IU/kg and severe bleeds were treated with 80 IU/kg. • In the case of minor surgery, a pre-operative dose of nonacog beta pegol 40 IU/kg was administered.	Safety Efficacy PK
Global	Study 3773	III	Patients with severe hemophilia B (13-70 years of age) who plans to undergo major surgery	N = 13 (n = 0)	Pre-operative dose: A dose of nonacog beta pegol 80 IU/kg prior to surgery Post-operative dose (within 1 to 6 days post-operative): Two doses of nonacog beta pegol 40 IU/kg Both the pre- and post-operative doses were adjusted according to the patients' blood FIX activity levels.	Efficacy Safety
Global	Study 3774 (main period)	III	Patients with severe hemophilia B (0-12 years of age)	N = 25 (n = 3)	Nonacog beta pegol 40 IU/kg once weekly. The same dosage regimen as that employed in Study 3747 was used for the treatment of bleeding episodes and for minor surgery.	Safety Efficacy PK

The summary of the major clinical studies is described below. The evaluation results of the PK data for each study are presented in "Section 6.2 Clinical pharmacology."

7.1 Phase I study

7.1.1 Global phase I study (CTD 5.3.3.2.1, Study 3639, conducted from August 2009 to July 2010)

A dose-escalation study was conducted at 17 sites in 8 countries including Japan to evaluate the safety and PK of nonacog beta pegol in patients aged ≥18 and ≤65 years with severe hemophilia B (FIX activity ≤2%) with no history of inhibitors who were previously treated patients with a history of ≥150 exposure days to FIX products (target sample size, 20 subjects [5 subjects per dose]).

Subjects received a single dose of their previously used (prior to participation in this study), currently available

FIX products at 25, 50, or 100 IU/kg, followed by a washout period of ≥7 days, and then a single dose of nonacog beta pegol at the same dose level.

Of the 18 subjects enrolled in this study, 16 received nonacog beta pegol (25 IU/kg, 6 subjects [0 Japanese subjects]; 50 IU/kg, 5 subjects [2 Japanese subjects]; 100 IU/kg, 5 subjects [1 Japanese subject]) and were included in the safety analysis set.

According to safety analyses, 11 AEs (25 IU/kg: 2 events of fatigue and 1 event each of tooth infection, hypersensitivity, nasopharyngitis, rhinitis, and myalgia; 50 IU/kg: 1 event each of overdose, joint stiffness, and epistaxis; 100 IU/kg: 1 event of dermatitis contact) were reported in 6 of 16 subjects (37.5%) within 4 or 5 weeks after administration of nonacog beta pegol.

Furthermore, 4 adverse drug reactions (ADRs) (25 IU/kg: 2 events of fatigue and 1 event each of hypersensitivity and myalgia) occurred in 2 subjects. The outcomes for all events were reported as resolved.

No death occurred. One serious adverse event (SAE) (hypersensitivity) occurred in 1 subject (25 IU/kg). This event was considered related to nonacog beta pegol by the investigator. The outcome was resolved, but the subject was withdrawn from the study.

The safety data were analyzed for Japanese subjects. Two AEs (50 IU/kg, epistaxis; 100 IU/kg, dermatitis contact) occurred in 2 subjects. No ADRs or SAEs occurred.

7.2 Phase III studies

7.2.1 Global phase III study (CTD 5.3.5.2.1, Study 3747, conducted from April 2011 to April 2013)

A single-blind, parallel-group study was conducted at 54 sites in 15 countries, including Japan, to evaluate the safety, efficacy, and PK of nonacog beta pegol in patients aged ≥13 and ≤70 years with severe hemophilia B (FIX activity ≤2%) with no history of inhibitors, who were previously treated patients with a history of ≥150 exposure days to other FIX products (target sample size: 68 subjects [routine prophylaxis group, ≥50 subjects; on-demand dosing group, ≥10 subjects]). This study was designed to include 2 routine prophylaxis groups (low- and high-dose groups) and 1 on-demand treatment group. The subjects were allowed to choose routine prophylaxis or on-demand treatment, and those who chose routine prophylaxis were randomly assigned to one of the two prophylaxis groups.

Subjects in the routine prophylaxis group and the on-demand treatment group (Table 17) were treated for 52 and 28 weeks, respectively. For a mild or moderate bleeding episode, a dose of nonacog beta pegol 40 IU/kg was administered for both treatment groups. If hemostasis was not achieved, the investigator had to be contacted before the administration of an additional dose of 40 IU/kg of nonacog beta pegol. For a severe bleeding episode, a dose of nonacog beta pegol 80 IU/kg was administered, and the subsequent treatment was provided at the discretion of the treating physician. For subjects undergoing minor surgery during the study

period, a pre-operative single dose of nonacog beta pegol 40 IU/kg was recommended. The maximum dose to be administered to a subject within 24 hours was 200 IU/kg with a maximum individual dose of 80 IU/kg. When an additional dose was to be given, the doses had to be separated by an interval of at least 1 hour.

Table 17. Dosing regimens

Treatment group		Dosage regimen
Routine prophylaxis	Low-dose	Nonacog beta pegol 10 IU/kg once weekly
	High-dose	Nonacog beta pegol 40 IU/kg once weekly
On-demand treatment		No routine prophylaxis with nonacog beta pegol

In this study, 74 subjects (routine prophylaxis [low dose] group, 30 subjects [including 4 Japanese subjects]; routine prophylaxis [high dose] group, 29 subjects [including 2 Japanese subjects]; and on-demand treatment group, 15 subjects [including 2 Japanese subjects]) were enrolled, and all of them received nonacog beta pegol and were included in the safety analysis set and full analysis set (FAS).

The number of days of exposure to nonacog beta pegol (mean ± SD [range]) per subject was 13.6 ± 8.7 (2, 31) days in the on-demand dosing group, 55.8 ± 10.6 (22, 75) days in the routine prophylaxis (low dose) group, and 52.6 ± 11.9 (7, 72) days in the routine prophylaxis (high dose) group.

The primary endpoint of this study was defined as (1) the incidence of inhibitory antibodies (inhibitors) against FIX. The secondary endpoints were defined as (2) hemostatic effect of nonacog beta pegol when used for treatment of bleeding episodes and (3) annualized bleeding rate (ABR) during routine prophylaxis. The endpoints were evaluated in an order of (1), (2), and (3) in a sequential manner when the previous criteria for the respective endpoints were satisfied.

The primary endpoint of this study was the incidence of inhibitory antibodies against FIX (≥0.6 Bethesda units [BU]) (the number of subjects who developed inhibitory antibodies / the total number of all subjects with ≥10 exposure days and any subjects with <10 exposure days but with inhibitory antibodies). None of the subjects developed inhibitory antibodies during the study period (0 of 67 subjects), and the upper limit of the one-sided 97.5% CI for the incidence of inhibitory antibodies against FIX was 6.0%, which fulfilled the prespecified criteria (incidence of ≤2%; the upper limit of one-sided 97.5% CI of ≤10.7%).

To evaluate the efficacy of nonacog beta pegol in the on-demand treatment of bleeding episodes, the hemostatic effect of nonacog beta pegol was assessed for a total of 341 bleeds by the subjects or their parents (legally acceptable representable) and the investigator according to the scale shown in Table 18.

Table 18. Scale for hemostatic effect of nonacog beta pegol

Excellent	Abrupt pain relief and/or clear improvement in objective signs of bleeding within 8 hours after a single injection
Good	Noticeable pain relief and/or improvement in signs of bleeding within 8 hours after a single injection
Moderate	Probable or slight beneficial effect within the first 8 hours after the first injection but requiring more than one injection within 8 hours
Poor	No improvement or worsening of symptoms within 8 hours after two injections

The success rate for the treatment of bleeding episodes (hemostatic response rated as “excellent” or “good”) was 92.4% (two-sided 95% CI: 87.0, 95.6), thus satisfying the prespecified criteria (the lower limit of two-sided 95% CI of >65%, logistic-regression analysis assuming independent working correlation matrix).

To evaluate the efficacy of routine prophylaxis, the ABR was assessed in the routine prophylaxis (high and low doses) groups. Table 19 shows the results of each treatment group. Only the routine prophylaxis (high dose) group fulfilled the prespecified criteria (the upper limit of two-sided 95% CI of ABR, <4.8).

Table 19. ABR (FAS)

		Routine prophylaxis (low dose) (N = 30)	Routine prophylaxis (high dose) (N = 29)
No. of subjects with bleeding episodes requiring treatment (n)		25	16
No. of bleeding episodes requiring treatment (bleeds)		132	70
ABR (bleeds/patient-year)	Mean ± SD	4.81 ± 5.41	3.53 ± 7.41
	Median (range)	2.93 (0.00, 18.13)	1.04 (0.00, 37.78)
	Estimate (two-sided 95% CI)[a)]	4.56 (3.01, 6.90)	2.51 (1.42, 4.43)

a) Poisson regression using treatment as a factor and treatment duration as an offset variable

According to safety analyses, 215 AEs were reported in 60 of 74 subjects (81.1%) during the period from the first dose of nonacog beta pegol until 4 weeks after the last dose (or until the end of this study for subjects who were transferred to another study). Table 20 shows the AEs occurring in ≥10% of subjects in any of the groups.

Table 20. AEs occurring in ≥10% of subjects in any of the groups (safety analysis set)

AE	Routine prophylaxis (low dose) (N = 30)		Routine prophylaxis (high dose) (N = 29)		On-demand treatment (N = 15)	
	n (%)	No. of AEs	n (%)	No. of AEs	n (%)	No. of AEs
Nasopharyngitis	7 (23.3)	9	3 (10.3)	4	0 (0.0)	0
Influenza	4 (13.3)	4	3 (10.3)	5	1 (6.7)	1
Upper respiratory tract infection	3 (10.0)	4	3 (10.3)	4	2 (13.3)	2
Fall	1 (3.3)	1	3 (10.3)	4	0 (0.0)	0
Pain in extremity	1 (3.3)	1	3 (10.3)	3	1 (6.7)	1
Neck pain	0 (0.0)	0	3 (10.3)	3	0 (0.0)	0
Oropharyngeal pain	0 (0.0)	0	3 (10.3)	3	1 (6.7)	1
Fatigue	3 (10.0)	3	2 (6.9)	2	1 (6.7)	1
C-reactive protein increased	4 (13.3)	4	0 (0.0)	0	0 (0.0)	0
Headache	2 (6.7)	2	3 (10.3)	7	2 (13.3)	3

A total of 19 ADRs occurred in 12 subjects (routine prophylaxis [low dose] group: 2 events of fatigue and 1 event each of incorrect dose administered, accidental overdose, headache, white blood cell count increased, laryngeal pain, and hot flush; routine prophylaxis [high dose] group: 2 events of overdose and 1 event each of incorrect dose administered, headache, fatigue, palpitations, ear pruritus, and pain in extremity; on-demand treatment group: 2 events of speech disorder developmental and 1 event of nausea). The outcome of the events was reported as resolved, except for 1 event each of fatigue (routine prophylaxis [low dose] group) and pain in the extremity (routine prophylaxis [high dose] group) that were reported as not resolved.

No death or AEs leading to study discontinuation occurred. Four SAEs occurred in four subjects (routine

prophylaxis [low dose] group: retroperitoneal hematoma; routine prophylaxis [high dose] group: hip fracture, skin ulcer, and abdominal pain). All of these events were considered unrelated to nonacog beta pegol, and the outcome of the events was reported as resolved, except for skin ulcer, which was reported as not resolved. The outcome of skin ulcer was reported as resolved after the end of the study.

During the study period, 8 subjects underwent 15 minor surgeries (including dental procedures). During the surgery, 2 AEs (varices esophageal and gingival ulceration) occurred in 2 subjects, but both events were considered unrelated to nonacog beta pegol.

According to an analysis of safety data from Japanese subjects, 21 AEs occurred in 7 of 8 subjects (87.5%). Two ADRs (fatigue in the routine prophylaxis [low dose] group and palpitations in the routine prophylaxis [high dose] group) occurred in two subjects. The outcome of fatigue was reported as not resolved, but the palpitations were reported as resolved. No SAEs were reported.

7.2.2 Global phase III study (CTD 5.3.5.2.3, Study 3773, conducted from June 2012 to February 2013)

An uncontrolled study was conducted at 40 sites in 17 countries including Japan to evaluate the efficacy and safety of nonacog beta pegol during surgery in patients aged ≥13 and ≤70 years with severe hemophilia B (FIX activity ≤2%) with no history of inhibitors, who were previously treated patients with a history of ≥150 exposure days to FIX products (target sample size, 12 subjects). The subjects were scheduled to undergo major surgery (including patients who were transferred from Study 3747 and Study 3775).

The treatment regimen was as below. The maximum dose to be administered to a subject within 24 hours was 200 IU/kg with a maximum individual dose of 80 IU/kg. When an additional dose was to be given, the doses had to be separated by an interval of at least 1 hour.

Pre-operative dose:

A single bolus dose of nonacog beta pegol 80 IU/kg was administered 15 minutes to 4 hours prior to the surgery. If needed, the dose of nonacog beta pegol could be adjusted to maintain the FIX activity at approximately 100% during surgery, according to the recommendation by the World Federation of Hemophilia (WFH) guidelines.

Post-operative dose:

A 40 IU/kg dose of nonacog beta pegol was administered 24 to 48 hours after the pre-operative dose, depending on the desired FIX activity level. Thereafter, the dose adjustment of nonacog beta pegol was recommended to maintain a FIX activity level of approximately 0.5 IU/mL, according to the recommendation by the WFH guidelines.

All 13 subjects included in this study received nonacog beta pegol and were included in the safety analysis set

and FAS. No Japanese subjects were included in this study.

The primary endpoint of the study was the hemostatic effect during surgery, which was evaluated by the surgeons, anesthesiologists, and investigators on the day of surgery, according to the scale shown in Table 21.

Table 21. Scale for hemostatic effect during surgery

Excellent	Better than expected/predicted in this type of procedure.
Good	As expected in this type of procedure.
Moderate	Less than optimal for the type of procedure but hemostatic response maintained without change of treatment regimen.
Poor	Bleeding due to inadequate therapeutic response with adequate dosing, and a change of regimen is required.

In the FAS, 13 surgeries were performed (5 cases of knee arthroplasty, 2 cases of wisdom teeth removal, and 1 case each of wart excision, internal fixation of fracture, ankle arthroplasty, tooth extraction, hip arthroplasty, and tendon operation). The success rate in the hemostatic effect during surgery (rated as "excellent" or "good") was 100% (13 of 13 surgeries).

Safety analyses were performed for AEs reported in the period from the first dose of nonacog beta pegol until 4 weeks after the last dose (or until the end of this study for subject who were transferred to another study). A total of 17 AEs (epigastric discomfort, nausea, oral mucosal erythema, vomiting, face edema, pyrexia, excoriation, fall, musculoskeletal discomfort, pain in extremity, hemorrhage, hypertension, anemia, conjunctival hemorrhage, serum ferritin increased, type 2 diabetes mellitus, and pruritus) were reported in 9 subjects.

Two ADRs (serum ferritin increased and pruritus) occurred in 2 subjects. The outcome of serum ferritin increased was reported as not resolved, but pruritus was reported as resolved.
No death, SAEs, or AEs leading to study withdrawal were reported.

7.2.3 Global phase III study (CTD 5.3.5.2.4, Study 3774 [main period], conducted from May 2012 to April 2014)

An uncontrolled study was conducted at 29 sites in 8 countries including Japan to evaluate the safety, efficacy, and PK of nonacog beta pegol in patients aged ≤12 years with severe hemophilia B (FIX activity ≤2%) with no history of inhibitors, who were previously treated patients with a history of ≥50 exposure days to FIX products (target sample size, 24 subjects [≥10 subjects aged ≤6 years and ≥10 subjects aged 7-12 years]).

Subjects received 40 IU/kg of nonacog beta pegol once weekly. The same dosing regimens as that employed in Study 3747 were used for the treatment of bleeding episodes and for minor surgery. This study consisted of a main period (≥52 weeks) followed by an optional extension period. The cutoff date (April 7, 2014) was the date when all patients completed the main period, and the data as of the cutoff date were assessed.

All 25 subjects included in this study (12 subjects aged 0-6 years [including 1 Japanese subject] and 13 subjects

aged 7-12 years [including 2 Japanese subjects]) received nonacog beta pegol and were included in the safety analysis set and FAS.

The number of exposure days to nonacog beta pegol (mean ± SD [range]) per subject was 63.5 ± 15.4 (10, 83) days.

The primary endpoint of this study was the incidence of inhibitory antibodies against FIX (≥0.6 BU) (the number of subjects who developed the inhibitory antibodies / the total number of all subjects with ≥10 exposure days and any subjects with <10 exposure days but with inhibitory antibodies). None of the subjects developed inhibitory antibodies during the study period (0 of 25 subjects), thus fulfilling the prespecified criteria (incidence of ≤5%).

For the secondary endpoints, the efficacy of nonacog beta pegol in on-demand treatment and routine prophylaxis was evaluated.

To evaluate the efficacy of nonacog beta pegol in the treatment of bleeding episodes, hemostatic response was assessed for a total of 42 bleeding episodes by the subjects or their parents (guardians) and the investigator according to the scale shown in Table 18. The success rate for the treatment of bleeding episodes (hemostatic response rated as “excellent” or “good”) was 92.9% (39 of 42 bleeds).

The ABR was assessed for the efficacy of routine prophylaxis. The results are shown in Table 22.

Table 22. ABR (FAS)

No. of subjects with bleeding episodes requiring treatment (n)		15
No. of bleeding episodes requiring treatment (bleeds)		42
ABR (bleeds/patient-year)	Mean ± SD	1.42±1.64
	Median (range)	1.00 (0.00, 6.51)
	Estimate (two-sided 95% CI)[a)]	1.44 (0.92, 2.26)

a) Poisson regression model using age (0-6 years of age, 7-12 years of age) as a factor and treatment duration as an offset variable

According to an analysis of safety data for the period from the first dose of nonacog beta pegol until 3 weeks after the last dose, 250 AEs occurred in 23 of 25 subjects (92.0%) in the main period. Table 23 shows the AEs occurring in at least 4 subjects.

Table 23. AEs occurring in at least 4 subjects (safety analysis set)

AE	No. of subjects (%)	No. of AEs
Cough	10 (40.0)	17
Contusion	8 (32.0)	17
Pyrexia	6 (24.0)	14
Nasopharyngitis	5 (20.0)	11
Excoriation	5 (20.0)	10
Upper respiratory tract infection	5 (20.0)	7
Vomiting	4 (16.0)	10
Head injury	4 (16.0)	9
Pharyngitis	4 (16.0)	4
Diarrhea	4 (16.0)	4
Seasonal allergy	4 (16.0)	4

A total of 8 ADRs (abdominal pain, diarrhea, nausea, infusion site pain, injection site pain, eosinophilia, headache, and wheezing) occurred in 4 subjects. The outcome of all of these events was reported as resolved.

No death or AEs leading to study discontinuation were reported. One SAE (food poisoning) occurred in 1 subject, but this SAE was considered unrelated to nonacog beta pegol. The outcome was reported as resolved.

During the study period, 1 subject underwent two minor surgeries (tooth extraction). No AEs were noted during the surgeries.

An analysis of safety data from Japanese subjects revealed 53 AEs occurring in 3 of 3 subjects. No ADRs or SAEs occurred.

7.R Outline of the review conducted by PMDA

7.R.1 Strategy for the review

The epidemiological backgrounds of factor IX-deficient patients including patients with hemophilia B, bleeding tendency in such patients, and the concept of FIX replacement for the episodic treatment or prophylaxis of bleeding are similar both in and outside of Japan, thus suggesting that intrinsic and extrinsic ethnic factors may have little effect on the efficacy and safety of nonacog beta pegol. Therefore, data from Study 3747 as the pivotal study and data from Study 3773 in patients undergoing surgery and Study 3774 in children aged ≤12 years were used to evaluate the efficacy of nonacog beta pegol in the control of bleeding (decrease in ABR) during prophylactic treatment and the hemostatic response in the treatment of bleeding episodes and during surgery. The safety of nonacog beta pegol was assessed on the basis of the incidence of AEs and the development of inhibitory antibodies for all clinical studies submitted.

7.R.2 Efficacy

7.R.2.1 Efficacy in treatment of bleeding episodes

In Study 3747 (in subjects aged 13-70 years), the success rate for treatment of bleeding episodes (hemostatic response rated as “excellent” or “good”) was 92.4% (two-sided 95% CI: 87.0, 95.6). However, when the CTD was being prepared after the completion of the clinical study report, it was turned out that the analysis for

hemostatic response had not been performed as originally planned (analysis that takes correlation within subjects). Because the analysis plan did not specify the working correlation matrix for assessing correlation, a post-hoc logistic-regression analysis was performed using an exchangeable correlation as a working correlation matrix to take correlation within subjects into account. The success rate for treatment of bleeding episodes was 92.2% (86.9, 95.4). When an autoregressive correlation was used as the working correlation matrix, the success rate was 92.5% (87.1, 95.7). Though they were the post-hoc analyses, these analysis procedures yielded the lower limit of two-sided 95% CIs exceeding the prespecified criterion (65%) that was accepted by the hemophilia specialist. In Study 3774 (in subjects aged ≤12 years), the success rate for the treatment of bleeding episodes (hemostatic response) was 92.9% (39 of 42 bleeds); this result showed a comparable efficacy with that in subjects aged ≥13 years in Study 3747. The success rate for treatment of bleeding episodes in the clinical studies of nonacog beta pegol was almost comparable with those for currently available FIX products (88% to 96%) (*Haemophilia*, 2016; 22: 381-8: *Haemophilia*, 2014; 20: 15-24).

Furthermore, the success rate for treatment of bleeding episodes with 1 or 2 doses of nonacog beta pegol was 97.4% (336 of 345 bleeds) in Study 3747 and 97.6% (41 of 42 bleeds) in Study 3774.

PMDA's view:
In Study 3747, a working correlation matrix to be used in the within-subject correlation analysis was not prespecified, and as a consequence, the hemostatic response analysis taking the correlation within subjects into account was not performed as originally planned. This was inappropriate. The applicant should have developed an appropriate analysis plan with clear instructions and should have conducted the analysis in accordance with the plan. Furthermore, the scientific rationale for the criterion of 65% was unclear; therefore, the appropriateness of assessment using such a criterion cannot be determined. However, the three kinds of analyses for Study 3747 presented by the applicant and the results of all clinical studies of nonacog beta pegol both showed high hemostatic response. On the basis of these results, the efficacy of nonacog beta pegol can be promising in the treatment of bleeding episodes in FIX-deficient patients, including pediatrics.

7.R.2.2 Efficacy during surgery

In Study 3773 and Study 3775, which was as an extension study of Study 3747 and Study 3773, the hemostatic effect was evaluated during surgery. The hemostatic effect during surgery was rated as "excellent" or "good" in all surgeries, including 16 major surgeries (13 surgeries in Study 3773 and 3 surgeries in Study 3775) and 18 minor surgeries (in Study 3775), except for 2 surgeries in which the hemostatic effect was not evaluated.

Given that FIX replacement is necessary for FIX-deficient patients undergoing surgery and that the hemostatic effect of nonacog beta pegol has been demonstrated, PMDA considers that the efficacy of nonacog beta pegol during surgery is promising in FIX-deficient patients, including pediatrics.

7.R.2.3 Efficacy in routine prophylaxis

The applicant' explanation about the rationale for the efficacy criterion for routine prophylaxis:
The efficacy criterion in the routine prophylaxis group in Study 3747 was to establish that the upper limit of two-sided 95% CI of ABR was <4.8 bleeds/patient-year (corresponding to a 60% reduction in ABR in patients with hemophilia B treated on demand [12 bleeds/patient-year]).

The ABR (12 bleeds/patient-year) in patients with hemophilia B treated on demand was estimated from the data from 4 reports (*J Intern Med.* 1998; 244: 515-22; *Haemophilia*. 2002; 8: 745-52; etc.). Recent clinical studies reported that the ABR in patients with hemophilia B treated on demand was 18.7 to 35.5 bleeds/patient-year (*N Engl J Med.* 2013; 369: 2313-23; *Haemophilia*. 2014; 20: 398-406; etc.); therefore, the ABR of 12 bleeds/patient-year is considered conservative. Furthermore, the ABR (mean ± SD) in the on-demand treatment group was 16.91 ± 10.92 bleeds/patient-year in Study 3747; thus, the ABR of 12 bleeds/patient-year in patients with hemophilia B without routine prophylaxis was considered appropriate.

The 60% reduction in ABR was recommended by the US Food and Drug Administration (US FDA) as a criterion. Furthermore, the hemophilia specialist provided the view that the 60% reduction in ABR, particularly a decrease from 12 to 4.8 bleeds/patient-year, was clinically significant.

On the basis of the study results, the applicant provided the following explanation about the efficacy of nonacog beta pegol for routine prophylaxis:
In Study 3747, some subjects receiving nonacog beta pegol 10 IU/kg once weekly had low ABRs. However, the ABR in the routine prophylaxis (low dose) group was 4.56 bleeds/patient-year (two-sided 95% CI; 3.01, 6.90), which did not fulfill the prespecified efficacy criterion (the upper limit of two-sided 95% CI of ABR, <4.8). By contrast, the ABR in the routine prophylaxis (high dose) group was 2.51 bleeds/patient-year (two-sided 95% CI; 1.42, 4.43), which fulfilled the criterion. The ABR of 2.51 bleeds/patient-year in the routine prophylaxis (high dose) group was similar to the 2.6 to 4.2 bleeds/patient-year reported in routine prophylaxis with the currently available FIX products (*Haemophilia*. 2014; 20: 398-406, *Haemophilia*.2014; 20: 15-24; etc.).

In Study 3774, the ABR was 1.44 bleeds/patient-year (two-sided 95% CI; 0.92, 2.26) in children aged ≤12 years treated with nonacog beta pegol for routine prophylaxis, which was comparable with the 3.69 bleeds/patient-year reported in children receiving currently available FIX products for routine prophylaxis (*Thromb Haemost.* 2016; 116: 659-68).

PMDA's view:
Although the applicant considered that the 60% reduction in ABR should have clinical significance as an efficacy criterion in Study 3747, but its rationale was not unclear. The efficacy criterion is unlikely to be optimal. However, the prespecified ABR of "4.8 bleeds/patient-year" in patients with hemophilia B on routine prophylaxis did not greatly differ from that in patients treated with currently available FIX products in

consideration of the clinical results of the currently available FIX products reported in the literature, the ABR in the on-demand treatment group in Study 3747, and the pre-study ABR in subjects who participated in Study 3747 without a history of previous routine prophylaxis treatment (14.0 bleeds/patient-year). Therefore, evaluating the efficacy of nonacog beta pegol using the relevant criterion was of some significance.

On the basis of the submitted clinical studies results, the efficacy of nonacog beta pegol in the routine prophylaxis of bleeding (40 IU/kg once weekly) is promising in FIX-deficient patients, including pediatrics.

7.R.2.4 Consistency in results between the overall population and Japanese population

Table 24 shows the efficacy results from the overall population and Japanese population in Study 3747 and Study 3774.

Table 24. Efficacy results in Japanese and overall populations (FAS)

Efficacy endpoint			N	Japanese population	N	Overall population
Study 3747						
Proportion of bleeds rated as "excellent" or "good"			8	93.8% (45/48 bleeds)	74	91.3% (315/345 bleeds)
ABR (bleeds/patient-year)	Routine prophylaxis (low-dose)	Median (range)	4	2.50 [0.00, 17.69]	30	2.93 [0.00, 18.13]
	Routine prophylaxis (high dose)	Median (range)	2	19.91 [2.04, 37.78]	29	1.04 [0.00, 37.78]
Study 3774						
Proportion of bleeds rated as "excellent" or "good"			3	100% (4/4 bleeds)	25	92.9% (39/42 bleeds)
ABR (bleeds/patient-year)	Median (range)		3	1.37 [0.00, 1.61]	25	1.00 [0.00, 6.51]

PMDA's view on the consistency in the efficacy results between the overall and Japanese populations are:
Although a very limited number of Japanese subjects were enrolled in Study 3747 and Study 3774, hemostatic effects were similar in the overall population and Japanese population. In Study 3747, the median ABR was higher in the routine prophylaxis (high dose) group of the Japanese population than in the overall population; this result was attributed to a high ABR (37.78) in one of the two Japanese subjects. The Japanese subject with a high ABR had 3 target joints and concurrent severe hemorrhagic arthritis, and experienced 72 bleeding episodes within 12 months prior to the study even though this subject was on routine prophylaxis with currently available FIX products. This subject met the discontinuation criteria (unwilling or unable to comply with the procedures of the clinical study) and was withdrawn from the study after receiving the fourth dose of nonacog beta pegol for routine prophylaxis. During the study period, the subject suffered from 3 mild or moderate bleeding episodes, but hemostasis was achieved after a single dose of nonacog beta pegol 43.1 IU/kg and rated as success for all bleeding episodes.

The effects of intrinsic and extrinsic ethnic factors on the efficacy of nonacog beta pegol were insignificant [see Section 7.R.1]. No specific trend was observed in the PK of nonacog beta pegol in the Japanese population compared with the overall population in the clinical pharmacology study [see Section 6.2]. Based on the above, the efficacy of nonacog beta pegol is promising in the Japanese population.

7.R.3 Safety

7.R.3.1 Safety of nonacog beta pegol

SAEs reported in clinical studies were as follows: 1 SAE in 1 subject (25 IU/kg, hypersensitivity) in Study 3639, 4 SAEs in 4 subjects (retroperitoneal hematoma in the routine prophylaxis [low dose] group; hip fracture, skin ulcer, and abdominal pain in the routine prophylaxis [high dose] group) in Study 3747, 1 SAE in 1 subject (food poisoning) in Study 3774, and 6 SAEs in 6 subjects (hepatocellular carcinoma, road traffic accident, fecaloma, local swelling, gastroenteritis, and femur fracture) in Study 3775. These SAEs were considered unrelated to nonacog beta pegol, except for hypersensitivity in Study 3639. The outcome of these SAEs was reported as resolved, except for skin ulcer (not resolved) in Study 3747 and hepatocellular carcinoma (death) in Study 3775.

An analysis was performed for the safety of nonacog beta pegol in pediatric patients. The incidence of AEs in children aged ≤12 years in Study 3774 was 92.0% (23 of 25 subjects), which was higher than the 81.1% (60 of 74 subjects) in subjects aged ≥13 and ≤70 years in Study 3747. The AEs reported more frequently in children aged ≤12 years than in subjects aged ≥13 years were cough, pyrexia, and trauma.

To evaluate information on an ongoing study, data from Study 3774 were analyzed as of the data cutoff date (December 31, 2017). A total of 5 SAEs (viral upper respiratory tract infections, wheezing, otitis media, device related infection, and hemoptysis) were reported in 2 subjects in the extension period of the study. However, all of these events were considered unrelated to nonacog beta pegol, and their outcomes were reported as resolved. In Study 3895 submitted as reference data (a study involving previously-untreated patients aged <6 years with severe hemophilia B [FIX activity ≤2%]), 21 SAEs occurred in 11 subjects (2 events each of factor IX inhibition and dental caries and 1 event each of device related infection, mouth hemorrhage, anaphylactic reaction, otitis media viral, pneumonia, nasopharyngitis, bronchiolitis, gastroenteritis viral, upper respiratory tract infections, cellulitis, cellulitis of male external genital organ, catheter site infection, accidental underdose, blood culture positive, catheterization cardiac, Henoch-Schonlein purpura, and poor venous access). Except for factor IX inhibition, anaphylactic reaction, and accidental underdose, these SAEs were considered unrelated to nonacog beta pegol. The outcomes of these events were reported as resolved, except for factor IX inhibition (not resolved) and catheterization cardiac (unknown).

PMDA's view:

The submitted clinical study results demonstrated no clear differences in the safety profiles of nonacog beta pegol between subjects aged ≥13 years and children aged ≤12 years. Therefore, nonacog beta pegol is also tolerable for children aged ≤12 years.

7.R.3.2 AEs reported for currently available FIX products

PMDA reviewed the development of FIX inhibitors and shock/anaphylaxis because these AEs were reported for currently available FIX products and for nonacog beta pegol in the clinical studies. Although thromboembolism has been reported for currently available FIX products as an AE, it has not been reported

for nonacog beta pegol in the clinical studies.

7.R.3.2.1 FIX inhibitors

The applicant's explanation about the development of FIX inhibitors:

In Studies 3747 and 3774, which were conducted in patients who had been previously treated with other FIX products, no subjects developed FIX inhibitors. In the ongoing Study 3895 in previously-untreated patients aged <6 years, 2 of the 32 subjects developed FIX inhibitors by the data cutoff date (December 31, 2017). Table 25 shows the clinical courses of these subjects.

Table 25. Clinical courses of the 2 subjects who developed FIX inhibitors

Subject	No. of exposure days to nonacog beta pegol up to the development of inhibitors (days)	Inhibitor titer	Continuation/ discontinuation of the study	Outcome	Remarks
A	4[a)]	High titer	Discontinued	Not resolved[c)]	The subject developed anaphylaxis immediately after the fourth dose of nonacog beta pegol, and the FIX inhibitor development was identified within the same day.
B	5	Low titer	Continuing[b)]	Not resolved	

a) The subject was exposed to the currently available FIX products for 2 days.
b) As of December 31, 2017, the administration of nonacog beta pegol has not been resumed.
c) The subject was positive for FIX inhibitors after 2 weeks.

The incidence of FIX inhibitors has been reported as approximately 7% in patients with severe hemophilia B who has not been treated with FIX products (*Thromb Haemost*. 2015; 113: 968-75). At present, the incidence of FIX inhibitors associated with nonacog beta pegol has been considered within the range of the information previously reported in patients with hemophilia B.

7.R.3.2.2 Shock/anaphylaxis

The applicant's explanation about shock/anaphylaxis:

In the clinical studies of nonacog beta pegol, the following ADRs related to allergic hypersensitivity reactions (e.g., rash) were reported: 1 ADR (hypersensitivity) in 1 subject in Study 3639, 1 ADR (pruritus) in 1 subject in Study 3773, 2 ADRs (eosinophilia and wheezing) in 1 subject in Study 3774 (main period), and 1 ADR (injection site rash) in 1 subject in Study 3775. One anaphylactic reaction occurred in one subject in Study 3895, but it resolved after steroid treatment.

PMDA's view:

Precautionary advice concerning the development of inhibitors, shock/anaphylaxis, thromboembolism should be contained in the package insert, etc., as in the case of currently available FIX products.

Patients with hemophilia B with a history of FIX inhibitors are likely to develop anaphylaxis by subsequent treatment with FIX products (*J Pediatr Hematol Oncol.* 1997; 19: 23-7). Given that inhibitors (neutralizing antibodies) against FIX may compromise the efficacy of nonacog beta pegol, the information on the

development of inhibitors are extremely important. At present, Study 3895 includes only 32 subjects who had not been treated with FIX products, and definitive conclusions concerning the incidence of FIX inhibitors associated with nonacog beta pegol cannot be drawn. Therefore, the applicant is required to appropriately and promptly provide healthcare professionals with information from the ongoing clinical studies and post-marketing information obtained.

7.R.4 Indication(s)

The clinical studies were conducted to evaluate the efficacy of nonacog beta pegol in the treatment of bleeding episodes, treatment in surgery, and routine prophylaxis in patients with hemophilia B (FIX activity ≤2%). On the basis of the data from the studies, PMDA determined that the efficacy of nonacog beta pegol is promising and that the clinical position of nonacog beta pegol is similar to those of currently available FIX products. Therefore, PMDA considers that the indication of nonacog beta pegol should be the "control of bleeding tendency in patients with factor IX deficiency" as in the case of currently available FIX products.

7.R.5 Dosage and administration

7.R.5.1 Establishment of dosing regimens for the treatment of bleeding episodes and surgery

The median dose (range) for the treatment of mild or moderate bleeding episodes to successful hemostasis was 42.3 IU/kg (20, 445 IU/kg) in Study 3747 and 43.0 IU/kg (21.9, 213.4 IU/kg) in Study 3774.

A severe bleeding episode was reported in Study 3747, and it was treated with 2 doses of nonacog beta pegol 41.6 IU/kg.

For minor surgery, the dosing frequency per surgery was 1 dose, and the dose ranged from 39.8 to 42.4 IU/kg in Study 3747. In Study 3774, the dosing frequency per surgery was 1 dose, and the dose was 45.1 IU/kg.

For major surgery, no subjects received any additional doses on the day of surgery, and 1 of 13 subjects did not receive any post-operative additional dose in Study 3773. The remaining 12 received the median (range) of 2.0 doses (1, 4 doses) between 1 and 6 days post-surgery, and the mean dose per injection was 41.1 IU/kg (range: 20.0, 42.4 IU/kg). The median (range) of dosing frequency between 7 and 13 days post-surgery was 2.0 doses (1, 3 doses), and the mean dose per injection was 41.9 IU/kg (range: 41.2, 42.4 IU/kg).

Since the proposed dosage and administration and the standard of dosing regimen were not consistent with those employed in the clinical studies, the applicant provided the following explanation: The dosage and administration of nonacog beta pegol was selected based on the dosing regimens used for treatment of most bleeding episodes and treatment in surgery in the clinical studies. Furthermore, on the basis of the predicted blood FIX activity levels calculated from the IR and $t_{1/2}$ of nonacog beta pegol, the proposed dosage and administration and the standard of dosing regimens should be appropriate.

PMDA's view:
The doses of 40 and 80 IU/kg were employed in the clinical studies for the treatment of bleeding episodes and for treatment in surgery, and the efficacy and safety of nonacog beta pegol at the dose levels were demonstrated in the studies. Therefore, the dosage and administration of nonacog beta pegol should be as follows: "The usual dosage is 40 or 80 IU/kg per dose." The standard of dosing regimens should be established according to the severity of bleeding and the type of surgery on the basis of the dosing regimens used in the clinical studies rather than those used in specific bleeding episodes or surgeries. Information on the standard of dosing regimens should be provided in the package insert or other materials.

In the clinical studies, some cases were rated as "poor" for the hemostatic effects even though a higher dose than the prespecified dose or multiple doses were administered for the treatment of bleeding episodes. Therefore, the package insert should advise that alternative appropriate treatment options should be considered in patients who failed to achieve adequate hemostatic response after treatment with the recommended dose level or multiple doses. Furthermore, advice on the upper limit of the dose and dosing frequency should be given based on the dosing regimens employed in the clinical studies.

7.R.5.2 Establishment of dosage and administration for routine prophylaxis
In Study 3747 in patients aged ≥13 years, the high-dose group (40 IU/kg once weekly) achieved the prespecified criteria of ABR as the efficacy endpoint [see Section 7.R.2.3]. Furthermore, the results of Study 3774 in patients aged ≤12 years demonstrated the efficacy and safety of 40 IU/kg once weekly for routine prophylaxis. Therefore, the proposed dosage and administration statement for routine prophylaxis is as follows: "The usual adult and pediatric dosage is 40 IU/kg once weekly."

On the basis of the applicant's explanation, PMDA considers that the dosage and administration for routine prophylaxis should be "40 IU/kg once weekly" regardless of the patients' age.

7.R.5.3 Injection rate
The protocols of all the clinical studies conducted specified that the reconstituted solution of nonacog beta pegol should be administered at a maximum injection rate of 4 mL/min.

The clinical study results showed no specific safety concerns about the specified method of administration; therefore, PMDA has concluded that the inclusion of "slow intravenous injection at a rate of ≤4 mL/min" in the dosage and administration is acceptable.

On the basis of the results of the review presented in Sections 7.R.5.1through 7.R.5.4, PMDA has concluded that the dosage and administration of nonacog beta pegol should be as follows:

Dosage and Administration
Refixia is administered intravenously after reconstitution of the powder with the whole amount of attached

solvent. Inject the reconstituted solution slowly at a rate of ≤4 mL/min.
The usual dosage is 40 or 80 IU/kg body weight per dose.
For routine prophylaxis, the usual dosage is 40 IU/kg body weight once weekly.

7.R.6 Post-marketing investigations

The applicant's explanation:
The applicant plans to conduct a use-results survey involving patients treated with nonacog beta pegol to evaluate the safety and efficacy of nonacog beta pegol in clinical practice.

Animal studies of PEGylation products revealed the vacuolation of macrophages in various organs and cells in the kidneys, liver, and choroid plexus epithelium (*Toxicol Pathol*. 2015; 43: 959-83, etc.). In the toxicity study of nonacog beta pegol, PEG was detected in the choroid plexus [see Section 5.2]. The Committee for Medicinal Products for Human Use expressed concerns about the long-term safety of nonacog beta pegol (particularly in children in the stage of brain development and physical growth). In response to this information, the applicant plans to extend Study 3774 and Study 3895 to evaluate the effects of long-term exposure to nonacog beta pegol (particularly on the choroid plexus of the brain, liver, and kidneys) in the post-marketing setting and to conduct a new post-marketing study outside Japan to collect information on the long-term safety of nonacog beta pegol in non-Japanese patients on routine prophylaxis in clinical practice. Although PEG was found in the choroid plexus in the toxicity study of nonacog beta pegol, no toxicological changes were identified. No particular safety concerns were raised in the clinical studies. At present, therefore, these findings are unlikely to pose a clear risk.

PMDA's view:
The clinical studies of nonacog beta pegol evaluated only a very limited number of Japanese subjects. Furthermore, there is limited experience with the use of nonacog beta pegol in clinical settings in Japan. Therefore, the relevant safety information should be collected in routine clinical practice. Furthermore, the toxicity study of nonacog beta pegol revealed PEG present in the choroid plexus and other tissues/organs. This finding cannot be not determined to be a clear risk at present; however, post-marketing information on the effects of long-term exposure to nonacog beta pegol in Japanese patients should be collected to assess its safety.

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 assessment is currently underway. Its results and the conclusion of PMDA will be reported in Review Report (2).

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

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

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

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the control of bleeding tendency in patients with factor IX deficiency and that the product has acceptable safety in view of its benefits. Furthermore, the product is clinically meaningful because it offers a new treatment option for patients with factor IX deficiency who need therapy for controlling bleeding tendency.

PMDA has concluded that the product may be approved if the product is not considered to have any particular problems based on the Expert Discussion's decision on the efficacy and safety of the product and post-marketing investigations.

Review Report (2)

April 26, 2018

Product Submitted for Approval

Brand Name	Refixia I.V. Injection 500
	Refixia I.V. Injection 1000
	Refixia I.V. Injection 2000
Non-proprietary Name	Nonacog Beta Pegol (Genetical Recombination)
Applicant	Novo Nordisk Pharma Ltd.
Date of Application	July 11, 2017

List of Abbreviations

See Appendix.

1. Content of the Review

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

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

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

1.1 Dosage and administration

The expert advisors raised the following comment on the conclusion of PMDA in Review Report (1):

- Although the dosage regimens of currently available rFIX products are similar to one another when used for the treatment of bleeding episodes and treatment in surgery, the dosing regimen of nonacog beta pegol is different from those of such rFIX. Healthcare professionals and patients should be advised to follow an appropriate dosing regimen according to the severity of bleeding or the type of surgery.

In view of the discussion above, PMDA requested the applicant to change the description in the dosage and administration as below and to provide appropriate advice to healthcare professionals and patients.

Dosage and Administration

Refixia is administered intravenously after reconstitution of the powder with the whole amount of the attached solvent. Inject the reconstituted solution slowly at a rate of ≤4 mL/min. See dosing guidelines in the table below.

		Dosage and Administration
Treatment of bleeding episodes	Mild to moderate	A dose of 40 IU/kg is recommended. Additional doses of 40 IU/kg can be given, depending on the patient's conditions.
	Severe or life threatening hemorrhages	A dose of 80 IU/kg is recommended.
Treatment in surgery	Minor surgery	A pre-operative dose of 40 IU/kg is recommended.
	Major surgery	A pre-operative dose of 80 IU/kg will be administered. If needed, additional dose(s) will be given to maintain the intraoperative blood FIX activity at approximately 100% (1 IU/mL). A post-operative dose of 40 IU/kg is administered 24 to 48 hours after the preoperative dose, depending on the desired blood FIX activity level. Repeated doses of 40 IU/kg may be given within the first 7 days after surgery to maintain the blood FIX activity level at approximately 50% (0.5 IU/mL).
Routine prophylaxis		A dose of 40 IU/kg once weekly is recommended.

1.2 Risk management plan (draft)

PMDA's view

The safety of PEG is described. The accumulation of PEG and vacuolation in the choroid plexus epithelial cells were noted in the repeated-dose toxicity study of nonacog beta pegol and 40 kDa PEG; however, no functional disorder was detected in the animals tested [see Sections 5.2 and 5.7.2]. In consideration of the results of the clinical studies of nonacog beta pegol and knowledge from other PEGylation products, these findings are unlikely to be regarded as a clear risk at present. Furthermore, nonacog beta pegol is expected to be used longer than the examined period in the clinical studies, and there is insufficient data for the long-term use of PEG, including the currently available PEGylation products, in children in the stage of brain development and physical growth. The missing information on long-term safety is important. Therefore, the applicant should keep collecting the information by conducting post-marketing pharmacovigilance activities.

The above conclusion of PMDA was supported by the expert advisors. The expert advisors also presented the following comments.

- Unlike currently available FIX products, nonacog beta pegol is a protein attached with PEG. Therefore, the applicant should inform healthcare professionals and patients that nonacog beta pegol may cause new ADRs that have not been reported with the use of currently available FIX products. In addition to the currently available information on the safety of PEG, information from post-marketing pharmacovigilance activities should also be provided to healthcare professionals and patients to ensure that they understand the risks and benefits of nonacog beta pegol before its use.
- Since only limited reagents are available for FIX activity measurement after the administration of nonacog beta pegol, the applicant should appropriately provide healthcare professionals with such information by presenting relevant materials.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for nonacog beta pegol should include the safety specifications presented in Table 26 and that the applicant should conduct the

additional pharmacovigilance activities and risk minimization activities presented in Tables 27, 28, and 29. In particular, the additional risk minimization activities in Table 27 should include the currently available safety information of PEG (the results of the repeated-dose toxicity study of nonacog beta pegol and 40 kDa PEG and the fact that the long-term data exceeding 2 years in humans have not yet been obtained at the time of completion of the review) and new information obtained in the post-marketing setting (information from surveillance, studies, literature, and reports). Furthermore, the information should be provided to healthcare professionals and patients.

The applicant answered that they would properly implement the risk management plan (draft). By using the pharmacovigilance activities presented in Tables 28 and 29, the effects of long-term exposure to PEG (plasma PEG levels and effects on neurologic, renal, and hepatic functions) will be assessed.

Table 26. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Shock, anaphylaxis • Development of inhibitors	• Thromboembolism • Inappropriate treatment caused by inappropriate methods of FIX activity measurement (under- or overestimation)	• Long-term safety
Efficacy specification		
Not applicable		

Table 27. 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 • Use-results survey (see Table 28) • Post-marketing clinical study (see Table 29)[a)]	• Early post-marketing phase vigilance • Preparation and provision of the materials for healthcare professionals • Preparation and provision of the materials for patients

a) After obtaining approval of nonacog beta pegol, Study 3774 and Study 3895 (ongoing) will be shifted to the post-marketing studies.

Table 28. Outline of the use-results survey (draft)

Objective	Long-term safety and efficacy of nonacog beta pegol in routine clinical practice
Survey method	Continuous survey
Population	Factor IX-deficient patients (all patients aged <12 years will be enrolled to the possible extent.)
Observation period	From the start of nonacog beta pegol administration to the end of the reexamination period (An appropriate period should be set so that each patient can be followed as long as possible, in consideration of the recovery of the survey sheet and tabulation time.)
Planned sample size	20 patients
Main survey items	Characteristics of patients, compliance with the dosing regimen of nonacog beta pegol, concomitant medications/therapies, laboratory tests (including FIX level, development of FIX inhibitors, renal/hepatic function, neurological examination, and plasma PEG level), AEs (including shock, anaphylaxis, and development of inhibitors), and efficacy

Table 29. Outline of the post-marketing clinical study

	Study 3774	Study 3895
Objective	Evaluation of safety, efficacy, and PK	Evaluation of safety and efficacy
Study design	Uncontrolled	Uncontrolled
Population	Patients with severe[a)] hemophilia B (aged <12 years at the time of enrollment)	Patients with severe[a)] hemophilia B without a treatment history (aged <6 years at the time of enrollment)
Evaluation period	Until all subjects reach 12 years old (up to November 2023)	Until all subjects are exposed to nonacog beta pegol for at least 100 days (up to October 2022)

Planned sample size	24 subjects	50 subjects
Primary endpoint	Incidence of FIX inhibitors	Incidence of FIX inhibitors

a) FIX activity ≤2%

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

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

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

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

The new drug application data (CTD 5.3.5.2-1, CTD 5.3.5.2-3, CTD 5.3.5.2-4, and CTD 5.3.5.2-7) were subjected to on-site GCP inspection in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The overall clinical studies were conducted according to the GCP. Therefore, PMDA concluded that there were no obstacles to conducting its review on the basis of the application documents submitted. The following issue was detected in a study site. Although it does not largely affect the overall study evaluation, the relevant study sites were notified of the.

Issue requiring corrective action

Study site

- Deviation from the protocol (incompliance with the specified procedures for reporting SAEs)

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication, and dosage and administration shown below, with the following condition. Since this product contains a new active ingredient, the reexamination period is 8 years. The product is classified as a biological product. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Indication(s)

Control of bleeding tendency in patients with factor IX deficiency

Dosage and Administration

Refixia is administered intravenously after reconstitution of the powder with the whole amount of the attached solvent. Inject the reconstituted solution slowly at a rate of ≤4 mL/min. See dosing guidelines in the table below.

		Dosage and Administration
Treatment of bleeding episodes	Mild to moderate	A dose of 40 IU/kg is recommended. Additional doses of 40 IU/kg can be given, depending on the patient's condition.
	Severe or life threatening hemorrhages	A dose of 80 IU/kg is recommended.
Treatment in surgery	Minor surgery	A pre-operative dose of 40 IU/kg is recommended.
	Major surgery	A pre-operative dose of 80 IU/kg is recommended. If needed, the dose may be adjusted to maintain the blood FIX activity level at approximately 100% (1 IU/mL) during surgery. A post-operative dose of 40 IU/kg is administered 24 to 48 hours after the pre-operative dose, depending on the desired blood FIX activity level. Repeated doses of 40 IU/kg may be given within the first 7 days after surgery to maintain the blood FIX activity level at approximately 50% (0.5 IU/mL).
Routine prophylaxis		A dose of 40 IU/kg once weekly is recommended.

Conditions for Approval

The applicant is required to develop and appropriately implement a risk management plan.

Appendix

List of Abbreviations

ABR	Annualized bleeding rate
AC	Affinity chromatography
[redacted]	[redacted]
aPTT	Activated partial thromboplastin time
AUC	Area under the curve
BeneFIX	BeneFIX®
BEV	Bovine entero virus
BU	Bethesda unit
C_{168h}	Plasma concentration 168 hours post dosing
C_{30min}	Plasma concentration 30 min post dosing
CAL	Cells at the limit of *in vitro* cell age
CHO	Chinese hamster ovary
CI	Confidence interval
CL	Clearance
Clo	*Clostridium*
C_{max}	Maximum plasma concentration
CMP-NAN	Cytidine-5'-monophospho-N-acetylneuraminic acid disodium salt
EDTA	Ethylenediamine tetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
eMuLV	ecotropic murine leukemia virus
FAS	Full analysis set
FDA	Food and Drug Administration
FIX	Coagulation factor IX
FIXa	Activated coagulation factor IX
FIX-KO	Coagulation factor IX knock out
FVIIa	Activated coagulation factor VII
FVIIIa	Activated coagulation factor VIII
FX	Coagulation factor X
FXa	Activated coagulation factor X
FXIa	Activated coagulation factor XI
Gla	Gamma-carboxylated
HCP	Host cell protein
[redacted]	[redacted]
HPLC	High performance liquid chromatography
IBRV	Infectious bovine rhinotracheitis virus
ICH	International conference on harmonisation of technical requirements for registration of pharmaceuticals
IgG	Immunoglobulin
IR	Incremental recovery
IU	International unit
MCB	Master cell bank
MRT	Mean residence time
MVM	Minute virus of mice
N9	Recombinant FIX produced as intermediate for nonacog beta pegol
Nonacog beta pegol	Nonacog Beta Pegol (Genetical Recombination)
NZW	New Zealand White
pdFIX	Plasma-derived coagulation factor IX
PEG	Polyethylene glycol
PETG	Polyethylene terephthalate glycol
PMDA	Pharmaceuticals and Medical Devices Agency

[redacted]	[redacted]
RCB	Research cell bank
rFIX	Recombinant coagulation factor IX
rFIXa	Activated recombinant coagulation factor IX
RP-HPLC	Reversed phase high performance liquid chromatography
SDS-PAGE	Sodium dodecyl sulfate-polyacrylamide gel electrophoresis
[redacted]	[redacted]
SE-HPLC	Size exclusion high performance liquid chromatography
Study 3639	Study NN7999-3639
Study 3747	Study NN7999-3747
Study 3773	Study NN7999-3773
Study 3774	Study NN7999-3774
Study 3775	Study NN7999-3775
Study 3895	Study NN7999-3895
[redacted]	[redacted]
$t_{1/2}$	Terminal half-life
TEG	Thromboelastography
TF	Tissue Factor
TGA	Thrombin Generation Assay
Vss	Volume of distribution at steady-state
WBCT	Whole blood clotting Time
WCB	Working cell bank
WFH	World Federation of Hemophilia