

Report on the Deliberation Results

November 26, 2013

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

[Brand name] NovoEight for Intravenous Injection 250, 500, 1000, 1500, 2000, and 3000

[Non-proprietary name] Turoctocog Alfa (Genetical Recombination) (JAN*)

[Name of applicant] Novo Nordisk Pharma Ltd.

[Date of application] December 27, 2012

[Results of deliberation]

In the meeting held on November 18, 2013, 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 re-examination period for the product is 8 years. Neither the drug substance nor the drug product is classified as poisonous drugs or powerful drugs, and the product is classified as a biological product.

* *Japanese Accepted Name (modified INN)*

This English version of the Japanese review report is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA will not be responsible for any consequence resulting from the use of this English version.

Review Report

October 31, 2013

Pharmaceuticals and Medical Devices Agency

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

[Brand name]	NovoEight for Intravenous Injection 250, 500, 1000, 1500, 2000, and 3000
[Non-proprietary name]	Turoctocog Alfa (Genetical Recombination)
[Name of applicant]	Novo Nordisk Pharma Ltd.
[Date of application]	December 27, 2012
[Dosage form/Strength]	Lyophilized powder for solution for injection: Each vial contains 250, 500, 1000, 1500, 2000, or 3000 International Units (IU) of Turoctocog Alfa (Genetical Recombination) to be used immediately after reconstitution.
[Application classification]	Prescription drug (1) Drug containing a new active ingredient
[Chemical structure]	
Molecular formula:	$C_{7480}H_{11379}N_{1999}O_{2194}S_{68}$
Molecular weight:	ca. 176,000
Chemical name:	Turoctocog alfa is a recombinant human blood coagulation factor VIII analog which corresponds to amino acid 1 to 750 and 1638 to 2332 of human blood coagulation factor VIII. Turoctocog alfa is a glycoprotein (molecular weight: ca. 176,000) composed of an H chain consisting of 761 amino acid residues and an L chain consisting of 684. Turoctocog alfa is produced by Chinese hamster ovary cells.
[Items warranting special mention]	None
[Reviewing office]	Office of Vaccines and Blood Products

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[Amino acid sequence]

Heavy chain (HC)

ATRRYYLGAV ELSWDYMQSD LGELPVDARF PPRVPKSFPP NTSVVYKKTL
FVEFTDHLFN IAKPRPPWMG LLGPTIQAEV YDTVVITLKN MASHPVSLHA
VGVSYWKASE GAEYDDQTSQ REKEDDKVFP GGSHTYVWQV LKENGPMASD
PLCLTYSYLS HVDLVKDLNS GLIGALLVCR EGSLAKEKTQ TLHKFILLFA
VFDEGKSWHS ETKNSLMQDR DAASARAWPK MHTVNGYVNR SLPGLIGCHR
KSVYWHVIGM GTTPEVHSIF LEGHTFLVRN HRQASLEISP ITFLTAQTLL
MDLGQFLLFC HISSHQHDGM EAYVKVDSQP EEPQLRMKNN EEAEDYDDDL
TDSEMDVVRF DDDNSPSFIQ IRSVAKKHPK TWVHYIAAEE EDWDYAPLVL
APDDRSYKSQ YLNNGPQRIG RKYKKVRFMA YTDETFKTRE AIQHESGILG
PLLYGEVGD TLLIIFKNQAS RPYNIYPHGI TDVRPLYSTR LPKGVKHLKD
FPILPGEIFK YKWTVTVEDG PTKSDPRCLT RYYSSFVNME RDLASGLIGP
LLICYKESVD QRGNQIMSDK RNVILFSVFD ENRSWYL TEN IQRFLPNPAG
VQLEDPEFQA SNIMHSINGY VFDSLQLSVC LHEVAYWYIL SIGAQTDFLS
VFFSGYTFKH KMVYEDTLTL FPFSGETVFM SMENPGLWIL GCHNSDFRNR
GMTALLKVSS CDKNTGDYYE DSYEDISAYL LSKNNAIEPR SFSQNSRHPS
QNPPVLKRHQ R

Light chain (LC)

EITRITLQSD QEEIDYDDTI SVEMKKEDFD IYDEDENQSP RSFQKKTRHY
FIAAVERLWD YGMSSSPHVL RNRAQSGSVP QFKKVVVFQEF TDGSFTQPLY
RGELNEHLGL LGPYIRAEVE DNIMVTFRNQ ASRPYSFYSS LISYEEDQRQ
GAEPRKNFVK PNETKTYFWK VQHMAPTKD EFDCKAWAYF SDVDLEKDVH
SGLIGPLLVC HTNTLNPAHG RQVTVQEFAL FFTIFDETCS WYFTENMERN
CRAPCNIQME DPTFKENYRF HAINGYIMDT LPGLVMAQDQ RIRWYLLSMG
SNENIHSIHF SGHVFTVRKK EEYKMALYNL YPGVFETVEM LPSKAGIWRV
ECLIGEHLHA GMSTLFLVYS NKCQTPLGMA SGHIRDFQIT ASGQYGQWAP
KLARLHYSGS INAWSTKEPF SWIKVDLLAP MIIHGIIKTQG ARQKFSSLYI
SQFIIMYSLD GKKWQTYRGN STGTLMVFFG NVDSSGIKHN IFNPPIIARY
IRLHPTHYSI RSTLRMELMG CDLNSCSMPL GMESKAISDA QITASSYFTN
MFATWSPSKA RLHLQGRSNA WRPQVNNPKE WLQVDFQKTM KVTGVTTQGV
KSLLTSMYVK EFLISSSQDG HQWTLFFQNG KVKVFQGNQD SFTPVVNSLD
PPLLTRYLRI HPQSWVHQIA LRMEVLGCEA QDLY

Disulfide bonds: Shown as solid lines

Sulfations: Y346, Y718, Y719 and Y723 of the HC, and Y16 and Y32 of the LC

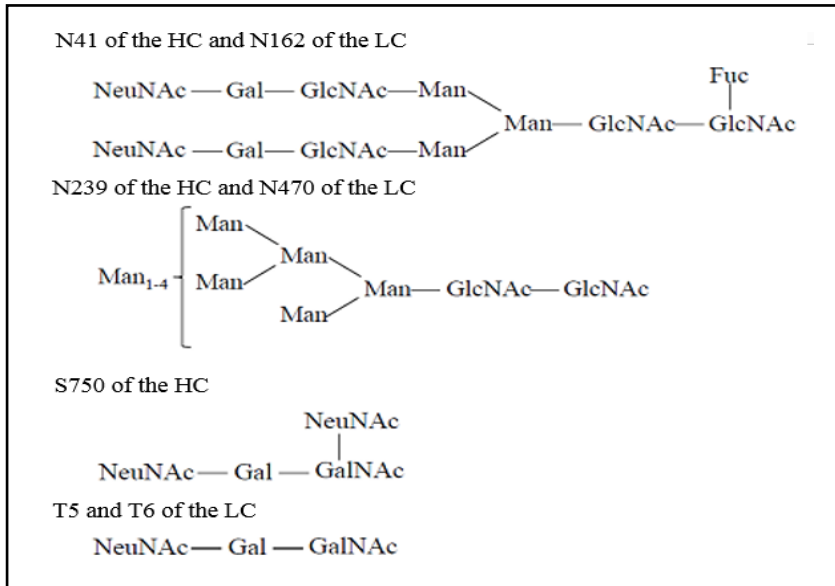
Partial processing: E1-S9 of the LC

Processing: R761 of the HC

Glycosylations: N41 and N239 of the HC, and N162 and N470 of the LC

Partial glycosylations: S750 of the HC, and T5 and T6 of the LC

Putative structures of major carbohydrate chains



NeuNAc: N-acetylneuraminic acid

Gal: galactose

GlcNAc: N-acetylglucosamine

Man: mannose

Fuc: fucose;

GalNAc: N-acetylgalactosamine

Review Results

October 31, 2013

[Brand name] NovoEight for Intravenous Injection 250, 500, 1000, 1500, 2000, and 3000

[Non-proprietary name] Turoctocog Alfa (Genetical Recombination)

[Name of applicant] Novo Nordisk Pharma Ltd.

[Date of application] December 27, 2012

[Results of review]

Based on the data submitted by the applicant, PMDA has concluded that the efficacy of turoctocog alfa in controlling bleeding tendency in patients with blood coagulation factor VIII deficiency has been demonstrated, and that its safety is acceptable in view of its observed benefits. However, PMDA considers that its long-term safety should be investigated further in post-marketing surveillance.

As a result of its regulatory review, PMDA concluded that the product may be approved for the following indication and dosage and administration.

[Indication] Control of bleeding tendency in patients with blood coagulation factor VIII deficiency

[Dosage and administration] The product should be reconstituted with the entire volume of the supplied solvent, and the reconstituted solution should be administered as a slow intravenous injection at a rate of 1 to 2 mL/min.

The usual dosage is 10 to 30 IU of turoctocog alfa per kg body weight for on-demand treatment of bleeding. The dose may be adjusted according to the patient's clinical condition.

For routine prophylaxis, the usual dosage is 20 to 40 IU of turoctocog alfa per kg body weight every other day or 20 to 50 IU of turoctocog alfa per kg body weight 3 times weekly. The dosage for pediatric patients <12 years of age is 25 to 50 IU/kg body weight every other day or 25 to 60 IU of turoctocog alfa per kg body weight 3 times weekly.

Review Report (1)

October 18, 2013

I. Product Submitted for Registration

- [Brand name] NovoEight for Intravenous Injection 250, 500, 1000, 1500, 2000, and 3000
- [Non-proprietary name] Turoctocog Alfa (Genetical Recombination)
- [Name of applicant] Novo Nordisk Pharma Ltd.
- [Date of application] December 27, 2012
- [Dosage form/Strength] Lyophilized powder for solution for injection: Each vial contains 250, 500, 1000, 1500, 2000, or 3000 International Units (IU) of Turoctocog Alfa (Genetical Recombination) to be used immediately after reconstitution.
- [Proposed indication] Control of bleeding tendency in patients with haemophilia A (congenital blood coagulation factor VIII deficiency)
- [Proposed dosage and administration]

The product should be reconstituted with the entire volume of the supplied solvent, and the reconstituted solution should be administered as a slow intravenous injection at a rate of 1 to 2 mL/min. The dosage and duration of the replacement therapy depend on the severity of factor VIII deficiency, the location and extent of the bleeding, and the patient's clinical condition.

One IU of factor VIII activity is equivalent to that quantity of factor VIII in 1 mL normal human plasma. The calculation of the required dose of factor VIII is based on the empirical finding that 1 IU of factor VIII per kg body weight raises the plasma factor VIII activity by 2 IU/dL. The required dose is determined using the following formula:

Required units (IU) = body weight (kg) × desired factor VIII rise (% or IU/dL) × 0.5 (IU/kg per IU/dL).

In the case of haemorrhagic events, the factor VIII activity should not fall below the plasma activity levels (in % of normal or IU/dL) listed in the following table during the period required to control the events. The amount to be administered and the frequency of administration should be oriented to the clinical effectiveness in the individual patient.

Table: Guide for dosing in bleeding episodes and surgery

Degree of haemorrhage/ Type of surgical procedure	Factor VIII level required (%) (IU/dL)	Frequency of doses (hours)/ Duration of therapy (days)
<u>Haemorrhage</u> Mild Early haemarthrosis, muscle bleeding or oral bleeding	20-40	Repeat infusion every 12-24 hours until the bleeding episode as indicated by pain is resolved or healing achieved
Moderate More extensive haemarthrosis, muscle bleeding or haematoma	30-60	Repeat infusion every 12-24 hours for 3-4 days or more until pain and acute disability are resolved
Major Life threatening haemorrhages	60-100	Repeat infusion every 8-24 hours until threat is resolved
<u>Surgery</u> Minor surgery including tooth extraction	30-60	Every 24 hours until healing is achieved
Major surgery	80-100 (pre- and post-operative)	Repeat infusion every 8-24 hours until adequate wound healing, then therapy for at least another 7 days to maintain a factor VIII activity of 30%-60% (IU/dL)

Routine prophylaxis

For long-term routine prophylaxis against bleeding in patients with severe haemophilia A, the usual recommended doses are 20 to 40 IU of factor VIII per kg body weight every second day or 20 to 50 IU of factor VIII per kg body weight 3 times weekly. For pediatric patients <12 years of age, doses of 25 to 50 IU of factor VIII per kg body weight every second day or 25 to 60 IU of factor VIII per kg body weight 3 times weekly are recommended.

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

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

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

Haemophilia A (congenital blood coagulation factor VIII deficiency) is a bleeding disorder that is caused by a quantitative decrease or qualitative abnormalities in blood coagulation factor VIII (FVIII) and may present serious bleeding episodes. The primary treatment for patients with haemophilia A is to administer adequate dose of FVIII to ensure normal haemostasis.

FVIII is a protein consisting of a heavy chain, composed of the A1, A2, and B domains, and a light chain, composed of the A3, C1, and C2 domains.

The currently available FVIII products that are approved in Japan are human plasma-derived FVIII products (Cross Eight M for Intravenous Injection and Cross Eight MC for Intravenous Injection marketed by the Japan Blood Products Organization, and Confact F for Injection marketed by Kaketsuken); a full-length recombinant FVIII product that is produced using fermentation media containing human plasma protein (Kogenate FS Bioset Injection by Bayer Yakuin, Ltd.); and a full-length recombinant FVIII product manufactured using the serum-free process (Advate for Injection by Baxter).

Turoctocog Alfa (Genetical Recombination) (hereinafter referred to as “turoctocog alfa”) is a recombinant FVIII where the B domain is truncated to a short segment of 21 amino acid residues. Turoctocog alfa was developed by Novo Nordisk A/S, Denmark, and is produced using a serum-free medium. B-domain truncated FVIII products have been developed to improve the efficiency of manufacturing. Once activated by thrombin, turoctocog alfa is converted into the same structure as endogenous activated FVIII, thereby exhibiting pharmacological effects as a blood coagulation factor.

As part of the clinical development program for turoctocog alfa, the phase I trial (NN7008-3522) was initiated in patients with severe haemophilia A in March 2009. A global phase III study (Trial NN7008-3543) began in April 2009 in patients with severe haemophilia A in a total of 15 countries including Japan.

On October 15, 2012, new drug applications for turoctocog alfa were submitted in Europe and the United States (U.S.), and the drug was approved in the U.S. on October 15, 2013. The U.S. is the only country that has approved turoctocog alfa so far.

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

Turoctocog alfa drug substance is a solution of the active ingredient turoctocog alfa in a buffer containing excipients which are the same in composition as those used in the proposed commercial formulation.

2.A.(1.1) Preparation and control of cell substrate

(a) Preparation of the master cell bank (MCB) and working cell bank (WCB)

A complementary DNA (cDNA) that encodes the wild-type FVIII gene was isolated from a cDNA library from human kidney cells. From the isolated cDNA, a gene fragment where the B-domain is truncated to a total of 21 amino acid residues consisting of 10 amino acid residues from the N-terminal region and 11 amino acid residues from the C-terminal region was prepared, and was inserted into a vector to generate an expression construct. [REDACTED]

Using this cell line, the research cell bank, master cell bank (MCB), and working cell bank (WBC) were generated.

(b) Control of cell banks

The MCB, WCB, end-of-production cells (EPC), and cells at the limit of *in vitro* cell age used for production (CAL) were subjected to characterization [e.g. studies to confirm the expression of the target protein (enzyme-linked immunosorbent assay, ELISA), cell viability, cell growth, the pattern of cDNA integration (Southern blot analysis), mRNA expression (Northern blot analysis), cDNA sequence, and identification of the cell line using cDNA copy number and isozymes], and the cell banking system was confirmed to be genetically stable. Purity testing comprised sterility test, mycoplasma testing, extended S⁺ L⁻ focus assay, transmission electron microscopy, reverse transcriptase assay, *in vitro* tests, *in vivo* tests, hamster antibody production test, mouse antibody production test, and bovine virus testing. As a result, no endogenous virus, adventitious viruses or non-viral adventitious agents except for type A or C retrovirus-like particles were detected.

Stability testing was performed for the MCB and WCB to establish appropriate storage conditions. While new WCBs may be established whenever necessary, there are no plans to prepare a new MCB.

2.A.(1.2) Manufacturing process

Table 2-1 outlines the manufacturing process of the drug substance. The drug substance is aliquoted into bulk containers made of low-density polyethylene.

The manufacturing process for the drug substance was subjected to a process validation in the scale of commercial production, and the validation has revealed that the manufacturing process is controlled appropriately.

Table 2-1. Manufacturing process for the drug substance

	Process	Intermediates/drug substance	In-process control tests
Fermentation	Inoculation of WCB		
	Propagation in seed laboratory		
	Propagation in bioreactors		Bioburden
	Cell culture in production bioreactor		Sterility testing, mycoplasma testing, virus free test, and bioburden
	Clarification of harvest		
Capture	Capture by mixed mode chromatography combining both hydrophobic and ion-exchange properties.	Store the eluate at -80°C	Content and bioburden
Purification	Affinity chromatography		Bioburden
	Anion exchange chromatography		Bioburden
	Virus clearance filtration (filter with a pore diameter of 20 nm)		Filtration flow rate, filter leakage test, filter integrity test
	Size exclusion chromatography and filtration (0.2 µm)	Drug substance (store at -80°C)	Bioburden

Critical steps and critical intermediates are indicated with gray shading.

2.A.(1).3 Adventitious agents safety evaluation

Raw materials of animal origin used in the manufacturing process for the drug substance are Chinese hamster ovary (CHO) cells, which are the host cells, and an anti-FVIII monoclonal antibody that is used during the purification process using affinity chromatography.

For CHO cells, the MCB, WCB, and CAL were subjected to purity tests [see “2.A.(1).1) Preparation and control of cell substrate”]. The cell culture media for the CHO cells was subjected to *in vitro* adventitious virus testing, mycoplasma testing, and sterility testing. Neither viruses nor non-viral adventitious agents were detected.

The MCB and CAL of the cell line that produces an anti-FVIII monoclonal antibody used in the purification process were subjected to purity tests (sterility testing, mycoplasma testing, extended S+L- focus assay, transmission electron microscopy, reverse transcriptase assay, *in vivo* tests, *in vitro* tests, hamster antibody production test, and bovine virus testing), and were qualified for production. The cell culture media for this cell line was subjected to *in vitro* adventitious virus testing. No infectious viruses were detected. The anti-FVIII monoclonal antibody is prepared without using materials derived from animals, and undergoes the purification process to inactivate and/or remove viruses. The purification process has been demonstrated to be capable of inactivating and/or removing such viruses.

The robustness of the viral clearance process was confirmed with viral clearance studies using model viruses (Table 2-2).

Table 2-2. Results of viral clearance studies¹

Manufacturing process	Virus reduction factor (log ₁₀)			
	eMuLV	MVM	Reo	BEV
Capture process ²	█	█	█	█
Affinity chromatography ³	█	█	█	█
Anion-exchange chromatography	█	█	█	█
Virus clearance filtration	█	█	█	█
Overall virus reduction factor	> 17.6	9.3	6.6	> 14.1

eMuLV, murine leukemia virus; MVM, minute virus of mice; Reo, Reovirus 3; and BEV, bovine enterovirus

1. Each test was duplicated, and the lower result was used.
2. Viral clearance by chromatography using ion exchange and hydrophobic resins and surfactants
3. Affinity chromatography using anti-FVIII antibody/carriers
4. Reduction in virus titer of the order of ≤ 1.0 was ignored.

2.A.(1.4) Manufacturing process development (comparability)

The major changes in the manufacturing process during the development of the drug substance are described below (The 4 different manufacturing methods are referred to as Manufacturing Processes A, B, C, and D [the proposed manufacturing process]).

- Change from Manufacturing Process A to B: A virus filter membrane was added
- Change from Manufacturing Process B to C: The drug substance formulation was changed from █ to █ (L-methionine, an antioxidant, was added, and the concentrations of the ingredients used in the drug substance formulation were increased █ fold)
- Change from Manufacturing Process C to D:
 █
 █

It was confirmed that the quality attributes of the drug substance are comparable before and after the above-mentioned three manufacturing process changes.

2.A.(1.5) Characterization

(a) Structure/Composition

i) Primary structure

- Amino acid composition analysis, N-terminal amino acid sequencing, trypsin peptide mapping, and thrombin mapping revealed that the primary structure of turoctocog alfa corresponded to the theoretical structure of FVIII.
- █
 █
- █
 █

ii) Secondary and tertiary structures (higher-order structures)

- Enzyme digestion and mass spectrometry analysis identified a total of 4 disulfide bridges in the HC and LC. Two cysteine residues in the HC and 1 cysteine residue in the LC were identified as free cysteines. The locations of these free cysteine residues and disulfide bridges were the same as those reported for the wild type FVIII.

- [REDACTED]
- [REDACTED]

iii) Post-translational modification (carbohydrate structure)

- N-linked glycosylation
Trypsin peptide mapping revealed N-linked glycosylation at Asn¹⁶² of the LC and Asn⁴¹ of the HC. The results of LC-MS analysis and anion-exchange chromatography of the deglycosylated protein indicated that the protein had mono- and di-sialylated, core-fucosylated biantennary structures, and high-mannose structures (Man 5 to Man 9).
- O-linked glycosylation
Trypsin peptide mapping and thrombin mapping revealed that there was an O-linked glycosylation in the C-terminal region of the HC (at Ser⁷⁵⁰ in the truncated B-domain of 21 amino acids), and this site was glycosylated with a doubly sialylated structure (GalNAc(-sialic acid)-Gal-sialic acid).
- Tyrosine sulfation
Thrombin mapping and trypsin peptide mapping revealed that 2 tyrosine residues in the LC (Tyr¹⁶ and Tyr³²) and 4 tyrosine residues in the HC (Tyr³⁴⁶, Tyr⁷¹⁸, Tyr⁷¹⁹, and Tyr⁷²³) were sulfated.

(b) Physicochemical properties

i) Molecular mass

- The results of molecular mass determination using LC-MS analysis and static light scattering were consistent with the theoretical molecular mass of the target protein after post-translational modifications.
- Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) of the protein before thrombin cleavage revealed 2 bands of about 92 and 83 kDa corresponding to the HC and LC of turoctocog alfa. [REDACTED]

ii) Liquid chromatography

- Reverse-phase high-performance liquid chromatography (RP-HPLC) revealed 2 major peaks corresponding to the HC and LC of turoctocog alfa. [REDACTED]
- Size-exclusion high-performance liquid chromatography (SE-HPLC) revealed peaks corresponding to dimers and high-molecular weight proteins (HMWP) in addition to the major peaks.

iii) Spectroscopic profiles

- Ultraviolet spectrum revealed a specific absorption maximum at about 280 nm with an average absorptivity of 1.51 mL/(mg·cm).

iv) Others

- The pH-dependent solubility profile of turoctocog alfa was determined by analyzing the content of the drug in solutions of different pH. The content of the drug did not change after storage at 5°C in the pH range from 5.7 to 7.5.
- The thermal stability of turoctocog alfa was determined using differential scanning calorimetry. Thermal denaturation of turoctocog alfa occurred at about [REDACTED]°C to [REDACTED]°C.
- The tendency to form protein aggregates was determined using dynamic light scattering. The average hydrodynamic radius (R_h) at an ambient temperature of 25°C was about [REDACTED] to [REDACTED] nm, but increased substantially at [REDACTED]°C as an increased temperature induces the formation of aggregates.

(c) Biological properties

The FVIII activity of turoctocog alfa was determined using the one-stage activated partial thromboplastin time (APTT) assay (clotting assay) and a two-stage chromogenic substrate assay (chromogenic assay).

(d) Product-related substances

[REDACTED]

(e) Impurities

i) Process-related impurities

[REDACTED]

It has been confirmed that all of the above-described process-related impurities are consistently removed in the manufacturing process. The levels of host cell proteins and anti-FVIII monoclonal antibody are controlled by the specifications set for the drug substance.

ii) Product-related impurities

2.A.(1.6) Control of drug substance

The specifications for drug substance comprise content, appearance, pH, identity (SDS-PAGE and HPLC), purity (), glycosylation charge profile, peptide map, microbial limits, bacterial endotoxins, potency, and specific activity.

2.A.(1.7) Stability of drug substance

Table 2-3 outlines the results of major stability studies of the drug substance.

Table 2-3. Results of stability studies of the drug substance

	Manufacturing process (formulation)	Number of lots tested	Storage conditions	Study period	Storage form
Long-term testing	Manufacturing Process	2	°C	months	Low-density polyethylene bottle with low density polyethylene cap
	Manufacturing Process	2		months	
	Manufacturing Process	3		months ¹	
	Manufacturing Process	3		months ¹	
Accelerated testing	Manufacturing Process	3	°C	weeks	
Stress testing	Manufacturing Process	2	°C	weeks	

1. Planned to be continued for up to months

No changes were observed during the accelerated testing.

Changes in pH affected the content of impurities as well as the content and biological activity of the drug substance.

[REDACTED]

PMDA has requested the applicant to submit the latest results of the currently ongoing long-term tests on the drug substance manufactured with Manufacturing Process █ (drug substance formulation █).

2.A.(2) Drug product

2.A.(2).1 Description and composition of the drug product and formulation development

The drug product is a lyophilized powder for solution for injection which contains 250, 500, 1000, 1500, 2000, or 3000 International Units (IU) of the active ingredient per vial. The drug product contains L-histidine, sucrose, polysorbate 80, sodium chloride, L-methionine and calcium chloride dihydrate as excipients. [REDACTED]

[REDACTED] The secondary packaging is a paper carton.

The dose pack contains a prefilled syringe of saline (JP) as the solvent for reconstitution.

2.A.(2).2 Manufacturing process

The manufacturing process for the drug product consist of the solution preparation, sterile filtration, filling, freeze-drying, testing, and storage steps. Solution preparation, sterile filtration, and filling steps are defined as critical process steps. The manufacturing process for the drug product was subjected to a process validation in the scale of commercial production, and the validation has revealed that the manufacturing process is controlled appropriately.

2.A.(2).3 Manufacturing process development (comparability)

The major changes in the manufacturing process during the pharmaceutical development are as follows.

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

The comparability of the quality attributes between pre- and post-change drug products has been confirmed for the above-mentioned four changes made to the manufacturing process.

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

The specifications for drug product comprise content, appearance, reconstitution time/solubility, water content, appearance of solution, pH, identification (SDS-PAGE), purity ([REDACTED]), antioxidants, osmolarity, foreign insoluble matter test, insoluble particulate matter test, endotoxins, sterility testing, and potency.

2.A.(2).5) Stability of the drug product

The stability tests of 250 IU and 3000 IU formulations produced at the commercial scale were conducted using a bracketing design to evaluate the stability at the extremes. Table 2-4 summarizes the results of major stability studies of the drug product.

Table 2-4. Results of stability studies of the drug product

	Manufacturing process (formulation) of the drug substance	Storage conditions	Number of lots tested	Storage form	Study period
Long-term testing (Condition 1)	Process █████	Stored at 5 ± 3°C, protected from light	████ and █████ IU products, 3 lots each	Colorless glass vial	24 months ¹
Long-term testing (Condition 2)		Stored at 5 ± 3°C for 18 months, then at 30 ± 2°C, 75 ± 5% RH for 6 months, protected from light in both conditions.			24 months ¹
Long-term testing (Condition 3)		Stored at 30 ± 2°C, 75 ± 5% RH, protected from light.			12 months
Long-term testing (Condition 4)	Process █████	Stored at 5 ± 3°C, protected from light.	████, █████, and █████ IU products, 1 lot each		████ months ¹
Long-term testing (Condition 5)		Stored at 5 ± 3°C for 18 months, then at 30 ± 2°C, 75 ± 5% RH for 6 months, protected from light in both conditions.			████ months ¹
Accelerated testing (Condition 1)	Process █████	Stored at 40 ± 2°C, 75 ± 5% RH, protected from light.	████ and █████ IU products, 3 lots each		6 months
Accelerated testing (Condition 2)	Process █████				
Photostability testing	Process █████	Stored at room temperature, an overall illumination of █████ lux·hr, and an integrated near ultraviolet energy of █████ W h/m ²	████ and █████ IU products, 1 lot each	Colorless glass vial with and without secondary package	27 hours

1: Studies planned to be continued for up to █████ months

In the long-term testing with Condition 1, all attributes other than the identification were tested. Although the results after 24 months of storage have not been submitted for insoluble particulate matter, sterility, endotoxins, and osmolarity, no changes were observed during the study period for the other test attributes.

In the long-term testing with Conditions 2 and 3 and the accelerated testing, no changes were observed during the study period in any test attributes including insoluble particulate matter, sterility, endotoxins and osmolarity for which no results after 24 months of storage were obtained in long-term tests with Condition 1.

[REDACTED]

PMDA has requested the applicant to submit the latest results of some ongoing long-term studies (Conditions 1, 4, and 5) of the drug product.

2.A.(3) Reference materials

[REDACTED]

[REDACTED]

[REDACTED] Reference materials are stored at [REDACTED] to [REDACTED] °C, and specifications have been established.

2.B Outline of the review by PMDA

As a result of its review based on the submitted data, PMDA has concluded that the drug substance and the drug product are controlled appropriately in terms of quality attributes other than stability. PMDA has requested the applicant to submit the latest results of long-term studies of the drug substance and the drug product, and will describe the results of the review based on the applicant's response in Review Report (2).

3. Non-clinical data

3.(i) Summary of pharmacology studies

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

In primary pharmacodynamic studies, turoctocog alfa was assessed for *in vitro* performance characteristics, as well as *in vivo* effects in achieving haemostasis and treating blood coagulation disorders in mice and dogs, and the results were submitted to PMDA. An article on the cofactor activity of turoctocog alfa was submitted as a reference document. In the submitted data, turoctocog alfa was compared with 2 recombinant blood coagulation factor VIII (FVIII) products, Advate from Baxter and Refacto from Wyeth, and 1 human plasma-derived FVIII product, Haemate from CSL Behring. (Note the names of suppliers are those at the time of these studies.) The results of studies in cynomolgus monkeys were submitted as part of the safety pharmacology data.

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

3.(i).A.(1).1 *In vitro* studies

As *in vitro* primary pharmacodynamic study data, the results from the following 4 studies and 1 published article were submitted. The applicant explained that the results of these studies indicated no difference in performance characteristics between turoctocog alfa and the conventional FVIII products.

(a) Thrombin generation (4.2.1.1.8)

The FVIII activity of 3 batches of turoctocog alfa was compared with those of Advate, Refacto and Haemate by means of the maximum rates of thrombin generation in a reconstituted cell-based model

and a plasma model. In the reconstituted cell-based model, a mixture of peripheral blood-derived monocytes, and platelets that express tissue factor upon lipopolysaccharide stimulation, coagulation proteins (blood coagulation factor VII, activated blood coagulation factor VII, blood coagulation factor X [FX], blood coagulation factor IX, blood coagulation factor XI, prothrombin, tissue factor pathway inhibitor, antithrombin III, and blood coagulation factor V) and CaCl_2 was prepared, and the thrombin generation rate in the presence of a FVIII product was determined. In the plasma model, a suspension of isolated platelets and FVIII deficient plasma was prepared, and the thrombin generation rate in the presence of a FVIII product, tissue factor and CaCl_2 was determined. The results indicated that turoctocog alfa increased the maximum thrombin generation rate in a dose dependent manner as did other FVIII products.

(b) Interaction with von Willebrand factor (VWF) (4.2.1.1.2, 4.2.1.1.5)

The interactions of von Willebrand factor (VWF), a carrier protein that forms a complex with FVIII in circulating blood and determines the stability of VIII in plasma, with turoctocog alfa, Advate and Refacto were studied using a surface plasmon resonance (SPR) assay, and an enzyme-linked immunosorbent assay (ELISA). The equilibrium dissociation constant (K_D) between a FVIII product and VWF was 0.35 nmol/L for turoctocog alfa and 0.29 nmol/L for Refacto when the SPR assay was used. When the ELISA was used, the K_D values between a FVIII product and VWF obtained in duplicated tests were 0.24 and 0.29 nmol/L for turoctocog alfa, 0.37 and 0.50 nmol/L for Advate, and 0.33 and 0.43 nmol/L for Refacto. The affinity of binding of turoctocog alfa to VWF was similar to that of the other FVIII products.

(c) Interaction between turoctocog alfa and anti-FVIII monoclonal antibodies (mAbs) (4.2.1.1.9)

The reactivity of turoctocog alfa, Advate, Refacto, and Haemate with anti-FVIII antibodies was evaluated using sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and Western blot assay. In the Western blot assay, murine mAbs against the heavy chain (HC) and light chain (LC) of FVIII were used as primary antibodies to determine the reactivity to antigen. In the SDS-PAGE and Western blot assay, thrombin cleavage was confirmed for turoctocog alfa, Advate, and Refacto. The reactivity to the primary antibodies that was detected as bands specific to the HC and LC in the Western blot assay was similar among turoctocog alfa, Advate, Refacto, and Haemate.

(d) FVIII binding kinetics to anti-FVIII mAbs by the SPR assay (4.2.1.1.4)

Interactions of turoctocog alfa, Advate, and Refacto with anti-FVIII mAbs, i.e., 3 mAbs against the LC's epitope (EHS2, EHS4, and EHS8), and 2 mAbs specific to the HC (1F2 and EHS5) were examined by the SPR assay. The K_D values for the 5 mAbs did not differ significantly among turoctocog alfa, Advate and Refacto (Table 3-1).

Table 3-1. K_D Values for anti-FVIII mAbs

mAb	FVIII	K_D (mol/L)	Standard deviation	Residual standard deviation
1F2	Turoctocog alfa	1.34E-10	3.44E-11	2.86
	Advate	2.53E-10	2.89E-11	2.63
	Refacto	1.07E-10	2.89E-11	2.43
EHS2	Turoctocog alfa	2.46E-09	3.79E-10	2.69
	Advate	3.33E-09	1.76E-09	2.52
	Refacto	2.72E-09	3.40E-10	2.38
EHS4	Turoctocog alfa	8.60E-10	1.93E-10	2.67
	Advate	1.26E-09	4.22E-10	2.54
	Refacto	7.63E-10	4.49E-10	2.66
EHS5	Turoctocog alfa	2.05E-09	6.00E-10	2.56
	Advate	2.27E-09	5.15E-10	2.49
	Refacto	1.89E-09	3.61E-10	2.56
EHS8	Turoctocog alfa	4.06E-10	7.89E-11	2.48
	Advate	4.37E-10	9.29E-11	2.21
	ReFacto	3.90E-10	1.04E-10	2.34

K_D represents the mean of triplicated results.

(e) Characterization of cofactor activity and rates of activation and inactivation of turoctocog alfa (Published article; Haemophilia 16: 878-87, 2010)

Turoctocog alfa and Advate were quantitatively assessed for the FVIII cofactor activity (i.e., the K_D between a FVIII product and activated blood coagulation factor IX and the rate of activation of FX [K_m and k_{cat}]), the rate of activation of FVIII by thrombin, and the rate of inactivation of activated blood coagulation factor VIII (FVIIIa) by activated protein C. No differences in these parameters were found between turoctocog alfa and Advate.

3.(i).A.(1).2 *In vivo* studies

The results of the following 3 *in vivo* primary pharmacodynamic studies were submitted. The applicant explained that the results of these studies demonstrated the haemostatic effect of turoctocog alfa.

(a) Effect in a tail bleeding model in mice with haemophilia A (4.2.1.1.3)

A tail bleeding model in FVIII knock-out (KO) mice with haemophilia A was used to investigate the haemostatic effect of turoctocog alfa. Eight groups of FVIII-KO mice ($n = 4/\text{sex}/\text{group}$) received either turoctocog alfa or Advate at 1, 5, 20, or 200 IU/kg. As control groups, the vehicle was administered to a group of FVIII-KO mice ($n = 4/\text{sex}/\text{group}$) and a group of normal C57BL/J6 mice ($n = 4/\text{sex}/\text{group}$). At 5 minutes after the administration, a 4-mm section of the tail tip was cut, and the tail was immersed in saline. Bleeding time during the 30-minute observation period (the sum of the durations of all bleeding episodes) and the blood loss (the amount of hemoglobin in the saline) were determined.

The bleeding time and blood loss in the FVIII-KO mice group receiving the vehicle were statistically significantly longer ($p < 0.001$) and higher ($p < 0.01$), respectively, than those in the normal C57BL/J6 mice group (with Dunn's post-hoc test and Kruskal-Wallis test, with a level of significance of 5%). In the FVIII-KO mice groups receiving turoctocog alfa or Advate at 200 IU/kg, the bleeding time and blood loss were similar to those in the normal C57BL/J6 mice group. Based on the dose-response curve, the dose giving half maximal effect (ED_{50}) in shortening bleeding time was calculated as 24 IU/kg for turoctocog alfa and 44 IU/kg for Advate, and ED_{50} in reducing blood loss was calculated as 33 IU/kg for turoctocog alfa and 33 IU/kg for Advate, with no significant difference between the 2 products ($p = 0.21$ and $p = 0.99$, respectively; F test with a level of significance of 5%). Negative correlations were observed between plasma FVIII activity at 35 minutes after administration and the bleeding time and blood loss (Spearman's rank correlation coefficient, $r = 0.69$ [$p < 0.0001$] and $r = 0.47$ [$p = 0.02$], respectively). In the groups receiving turoctocog alfa and Advate, no haemostatic effects of either drug was observed at the dose of 1 IU/kg, and animals in the 5 and 20 IU/kg groups showed considerable within-group variance. There were no significant differences between these 3 groups and the vehicle control group (Dunn's post-hoc test and Kruskal-Wallis test with a level of significance of 5%).

(b) Effects in a knee injury model in mice with haemophilia A (4.2.1.1.7)

The effect of turoctocog alfa in a knee injury model in FVIII-KO mice was evaluated. A dose of turoctocog alfa 200 IU/kg, Advate 200 IU/Kg or the vehicle was administered intravenously to FVIII-KO mice ($n = 12/\text{sex}/\text{group}$) via the tail vein. Five minutes later, the right knee joint cavity was punctured with a 30G needle under anesthesia to induce joint bleeding. At 1 and 3 days after puncture, 12 mice ($n = 6/\text{sex}/\text{group}$) were euthanized. The right (punctured) and left (control) knee joint diameters were measured immediately after joint puncture and immediately before euthanasia. At the time of euthanasia, the punctured knee joint was surgically exposed and examined by microscopy. The severity of bleeding was graded according to the visual bleeding score (VBS), with a score range from 0 to 3, developed by Valentino. VBS scores and joint diameters (mean \pm standard deviation [SD]) were analyzed using two-way analysis of variance (ANOVA) with a level of significance of 5%.

The change in joint diameter before and at 3 days after puncture was significantly lower in the turoctocog alfa group (0.32 ± 0.39 mm) and the Advate group (0.25 ± 0.39 mm) than the vehicle control group (1.23 ± 0.94 mm, $p < 0.01$ and $p < 0.001$), but there was no significant difference between the turoctocog alfa and Advate groups. The VBS in the turoctocog alfa group (0.59 ± 0.93) and the Advate group (0.50 ± 1.06) was significantly lower than that in the vehicle control group (2.04 ± 1.3) ($p < 0.001$).

(c) Effects in haemophilia A dogs (4.2.1.1.6)

In a crossover study, 2 male dogs with haemophilia A received single doses of turoctocog alfa and Advate at 100 IU/kg in a crossover design with a washout period of 2 days. FVIII activity of the 2

drugs was determined with a method using a synthetic chromogenic substrate (referred to as the "chromogenic assay"), the one-stage clotting assay, whole blood clotting time, blood coagulation analysis (clotting time and clot formation), and APTT. Both drugs normalized these measures, which returned to baseline levels over time in a similar time course. One haemophilia A dog suspected to have neutralizing antibodies to FVIII had a lower *in vivo* recovery of FVIII, shorter half-life, and faster return of whole blood clotting time to the baseline level as compared with the other haemophilia A dog.

3.(i).A.(2) Secondary pharmacodynamic study

No secondary pharmacodynamic studies were conducted.

3.(i).A.(3) Safety pharmacology studies (4.2.3.1.1, 4.2.3.2.2)

Safety pharmacology was evaluated in a non- Good Laboratory Practice (GLP), single dose toxicity study in male cynomolgus monkeys (Study No. 207402) and a GLP-compliant, repeated-dose intravenous toxicity study (Study No. 208012) [see "3.(iii).A.(1) Single dose toxicity studies and (2) Repeat dose toxicity studies"]. As the single dose toxicity study on the effect of a single dose of turoctocog alfa on the cardiovascular system (Study No. 207402) was not performed in compliance with the principles of GLP, the data of the study are reviewed only as a reference. The applicant explained that the results of these studies did not indicate any effects of turoctocog alfa on the following parameters.

3.(i).A.(3.1) Central nervous system/general behavior

Animals were observed daily for signs of morbidity and overt toxicity, and were given a clinical examination at weekly intervals and post-administration observation immediately and at 0.5, 1, 2, and 4 hours after the return to the cage. Animals were also examined for neurological or central nervous pharmacological effects at baseline and on Day 3.

3.(i).A.(3.2) Respiratory function

Animals were observed for respiratory rate and depth (gross examination) at baseline, and 1 to 2 hours post-dose on Day 1 and 1 to 2 hours post-dose at Week 2.

3.(i).A.(3.3) Renal function

The effects of turoctocog alfa on renal function were assessed by clinical chemistry (at baseline, Day 14, and the end of the recovery period) and urinalysis (at baseline and week 2 of treatment).

3.(i).A.(3.4) Cardiovascular system

(a) Effect of single-dose administration

Blood pressure and electrocardiography (ECG) were recorded twice before administration (including one immediately before administration) and 3 times after administration (10 minutes, 4 hours, and 24

hours after administration) to investigate the effects of turoctocog alfa on blood pressure, pulse rate, and waveforms and intervals in ECG.

(b) Effects of repeat-dose administration

Blood pressure and electrocardiography were recorded at baseline, Day 1, and Week 2 at 1 to 2 hours post-dose to investigate the effects of turoctocog alfa on blood pressure, pulse rate, and waveforms and intervals in ECG.

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

PMDA requested the applicant to explain the reason why the single dose toxicity study on the safety pharmacology for the cardiovascular system (Study No. 207402) was not conducted in compliance with GLP, and the possible effects of non-compliance with GLP on the evaluation of turoctocog alfa.

The applicant responded that Study No. 207402 was a non-GLP study as it was conducted to select doses to be evaluated in the repeat dose intravenous toxicity study (Study No. 208012), and that the non-GLP status in Study No. 207402 should not affect evaluation as the 2 studies investigated the same test items and obtained similar results.

PMDA accepted the applicant's response since safety pharmacology of turoctocog alfa in the cardiovascular system may be assessed according to the results of the repeated dose intravenous toxicity study (Study No. 208012).

PMDA has concluded that the submitted results of the studies on primary pharmacodynamics demonstrate that the drug possesses an FVIII activity comparable to conventional FVIII products, and is expected to ensure haemostasis in the living body. PMDA also has concluded that the submitted results of safety pharmacology studies indicate no safety concerns with turoctocog alfa.

3.(ii) Summary of pharmacokinetic studies

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

The results of studies in mice, dogs, rats, and cynomolgus monkeys were submitted for regulatory review. The FVIII activity of turoctocog alfa in plasma samples was determined using the chromogenic assay. The lower limit of quantification of this assay was 40, 56, and 10.0 mIU/mL in mice, dogs, and rats, respectively, while that in cynomolgus monkeys was 0.053 and 1.00 IU/mL in the single-dose administration study (Section 4.2.2.2.1) and in the repeated-dose administration study (Section 4.2.3.2.2), respectively. FVIII antigen levels in mice plasma samples were determined by ELISA. The lower limit of quantification of the assay was 25 mIU/mL. Following administration of ¹²⁵I-turoctocog alfa to mice, plasma radioactivity levels were determined using a liquid scintillation counter, and tissue radioactivity levels by a quantitative whole body autoradiography. The lower limits of quantification of these 2 methods were 0.037 Bq and 0.37 Bq/mg, respectively. The levels of

anti-FVIII antibodies in plasma samples obtained from rats and cynomolgus monkeys were determined using a radioimmunoassay, and the neutralizing effect of anti-FVIII antibodies on FVIII activity in plasma samples collected from cynomolgus monkeys was measured using the chromogenic assay.

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

3.(ii).A.(1).1) Single dose study (4.2.1.1.6, 4.2.2.2.1, 4.2.3.1.1)

FVIII-KO mice (n = 12/sex/group for turoctocog alfa, and n = 10/sex/group for Refacto and Advate) received single intravenous doses of turoctocog alfa at a dose of 8, 80, 180 or 280 IU/kg, or Refacto or Advate (2 recombinant FVIII products commercially available in foreign countries) at a dose of 280 IU/kg. The FVIII activity level and FVIII antigen concentration in plasma samples obtained at a total of 9 time points, at baseline and from 5 minutes to 40 hours after administration were determined in 68 mice in the 6 groups.

The applicant discussed the results as follows:

In FVIII-KO mice, the systemic exposure to turoctocog alfa increased in a dose-dependent manner. When the chromogenic assay was used to determine the activity of FVIII, the systemic exposure to turoctocog alfa at a dose of 8 IU/kg was about 30% of the value expected from the measurements at doses from 80 to 280 IU/kg. This unexpectedly low exposure was considered to be caused by protein absorption into the container used for administration of the drug or the low FVIII activity level, which was near the lower limit of quantitation, in this group. The differences in pharmacokinetic parameters of turoctocog alfa at a dose of 8 IU/kg between the ELISA and the chromogenic assay were attributable to a difference in the lower limit of quantitation between the 2 assays.

A comparison of pharmacokinetic parameters of turoctocog alfa, Refacto, and Advate at a dose of 280 IU/kg revealed that the peak plasma FVIII activity level (C_{max}) measured using the chromogenic assay was higher for Advate than for turoctocog alfa and Refacto, but there were overlaps in the 95% confidence interval between the treatment groups. There were no important differences among the 3 FVIII products in elimination half-life ($t_{1/2}$), total body clearance (CL), or steady-state volume of distribution (V_{ss}). Consequently, the applicant considered that the pharmacokinetics of these 3 FVIII products were similar (Table 3-2).

Table 3-2. Mean pharmacokinetic parameters in FVIII-KO mice

	Chromogenic assay						ELISA					
	Turoctocog alfa				Advate	Refacto	Turoctocog alfa				Advate	Refacto
Dose (IU/kg)	8	80	180	280	280	280	8	80	180	280	280	280
AUC _{0-∞} (h·IU/mL)	0.16	7.1	20	26	28	29	0.96	3.6	10	20	17	20
C _{max} (IU/mL)	0.03	1.04	1.96	2.74	4.26	2.87	0.03	0.49	1.12	2.01	2.64	1.99
CL (mL/h/kg)	50	11	9	11	10	10	8	22	18	14	17	14
V _{ss} (mL/kg)	264	73	90	117	108	97	25	231	162	185	257	159
t _{1/2} (h)	3.6	4.9	7.2	7.8	7.3	6.7	21	7.4	6.8	9.6	11	8.2

AUC_{0-∞}: Area under activity (concentration) versus time from zero hours to infinity

Pharmacokinetic parameters were calculated from mean FVIII activity in animals at each time point

In the crossover study in haemophilia A dogs, 2 male dogs received single-dose intravenous administrations of turoctocog alfa and Advate at 100 IU/kg in a crossover design with a washout period of 2 days. FVIII activity in plasma was measured at baseline and 5, 15, and 30 minutes, and 1, 2, 3, 4, 6, 8, 12, 24, 32, 48, 56, 72, 80, 96, and 104 hours after administration of each drug. According to the applicant's explanation, a comparison of pharmacokinetic parameters between turoctocog alfa and Advate revealed that the pharmacokinetics profiles of the 2 drugs were similar between the animals. Regarding the fact the C_{max} and recovery of turoctocog alfa and Advate were lower in 1 animal (Dog 1) than the other animal (Dog 2), the applicant considered that the possible presence of anti-FVIII antibodies before treatment in Dog 1 was attributable to the difference between the 2 animals (Table 3-3).

Table 3-3. Actual pharmacokinetic parameters in haemophilia A dogs

		C _{max} (IU/mL)	AUC _{0-∞} (h·IU/mL)	t _{1/2} (h)	CL (mL/h/kg)	V _{ss} (mL/kg)	MRT (h)	Recovery (%)
Dog 1	Turoctocog alfa	1.26	7.2	7.2	13.4	123	9	59
	Advate	1.35	11.0	7.9	9.5	98	10	67
Dog 2	Turoctocog alfa	2.33	23.0	10.5	4.3	62	14	110
	Advate	2.70	22.0	8.2	4.5	47	11	123

MRT, mean residence time; Recovery, the percentage of increase in FVIII activity at C_{max} to the dose of the test drug

The single dose intravenous toxicity study in cynomolgus monkeys was conducted to investigate the toxicokinetics of turoctocog alfa. Six male cynomolgus monkeys received single intravenous doses of turoctocog alfa at 50, 250, 500, 1250, 2500, and 5000 IU/kg. Each animal received 2 different doses of turoctocog alfa on two separate days. Animals receiving turoctocog alfa at 50, 250, and 2500 IU/kg as the first dose received turoctocog alfa at 500, 1250, and 5000 IU/kg, respectively, 7 days after administration of the first dose. FVIII activity in plasma was measured at baseline and 0.25, 2, 6, 12, and 24 hours after the administration of turoctocog alfa. Systemic exposure to turoctocog alfa was not confirmed in 1 animal given 50 IU/kg. The applicant considered that this was due to high pre-dose plasma FVIII activity in this animal. The analysis of the data of 5 animals, excluding the animal in whom systemic exposure was not confirmed after the administration at 50 IU/kg revealed that plasma FVIII activity at 0.25 hours after administration increased almost in a dose-proportional manner. However, the area under the activity versus time curve from zero hours to 24 hours (AUC_{0-24h})

increased at high doses, but the increase was less than proportional to dose. The applicant considered that the increase in AUC_{0-24h} less than proportional to dose was caused by the development of neutralizing antibodies against FVIII due to repeated exposure to turoctocog alfa with dose titration design.

3.(ii).A.(1).2 Repeat dose studies (4.2.3.2.1, 4.2.3.2.2)

The toxicokinetics of turoctocog alfa was investigated in repeat dose studies in rats and cynomolgus monkeys.

A total of 60 rats in 4 groups (n = 9/sex/treatment group, and n = 3/sex in the control group) received the vehicle (0) or 50, 250, or 1250 IU/kg/day of turoctocog alfa intravenously for 14 days. On Days 1, 8 and 14, plasma FVIII activity was determined at pre-dose and 0.25, 2, 6, 12, and 24 hours post-dose. The plasma FVIII activity in animals in the turoctocog alfa group during 2 to 6 hours post-dose on Day 1 was higher than endogenous FVIII activity in animals in the control group during the same period, and higher than that in the treatment groups before the first dose of turoctocog alfa, which demonstrated exposure to the drug. However, on or after Day 8, the plasma FVIII activity and AUC_{0-24h} in animals in the turoctocog alfa group did not differ significantly from endogenous FVIII activity and AUC_{0-24h} in the control group. The applicant considered that this was caused by the generation of neutralizing antibodies as studies have indicated anti-turoctocog alfa antibodies are produced in animals receiving the drug.

A total of 29 cynomolgus monkeys in 4 groups (n = 8 males/treatment group, and n = 5 males in the control group) received the vehicle (0), or turoctocog alfa at 50, 1000, or 5000 IU/kg/day intravenously for 14 days. The plasma FVIII activity was determined at pre-dose and 0.25, 2, 6, 12, and 24 hours post-dose on Days 1 and 14. On Day 1, exposure to turoctocog alfa was demonstrated for 24 hours after administration in the 1000 and 5000 IU/kg groups. However, on Day 14, no apparent exposure to turoctocog alfa was observed. The applicant considered that the development of neutralizing antibodies affected the results as studies have indicated that treatment with turoctocog alfa induces the development of anti-turoctocog alfa antibodies that neutralize the drug.

3.(ii).A.(2) Distribution (4.2.2.3.1)

Nine male mice received ¹²⁵I-turoctocog alfa intravenously at a dose of 295 IU/kg. The levels of radioactivity in plasma and tissues was measured at 15, 30, and 90 minutes post-dose, and the tissue/blood radioactivity ratio was calculated. After the administration of ¹²⁵I-turoctocog alfa to mice, a high level of radioactivity was present in organs with high blood flow such as the liver, kidney, lung, and spleen. The tissue/blood radioactivity ratio was high in the thyroid at 30 minutes post-dose and thereafter. The applicant discussed as follows: These results suggest that turoctocog alfa does not accumulate in specific organs since the tissue/blood radioactivity ratio throughout the observation period was <1 in all tissues examined other than the thyroid, and the high tissue/blood radioactivity ratio in the thyroid is considered to reflect the accumulation of free iodine-125 in the thyroid.

The applicant explained the reason why plasma and tissue radioactivity was measured only for the first 90 minutes after the administration of ¹²⁵I-turoctocog alfa as follows: It is likely that tyrosine residues in ¹²⁵I-turoctocog alfa are reactive to tyrosine iodine-125 in the living body, and that free iodine-125 is released from the radiolabeled turoctocog alfa in a short period of time. The change over time in the tissue/blood radioactivity ratio for the thyroid suggests that a large amount of iodine-125 has been released from the drug and accumulated in the thyroid at 90 minutes after administration. The applicant thus considered that it would be difficult to evaluate the accumulation and clearance of ¹²⁵I-turoctocog alfa appropriately at later time points.

3.(ii).A.(3) Metabolism

No studies on metabolism of turoctocog alfa were performed.

3.(ii).A.(4) Excretion

No studies on excretion of turoctocog alfa were performed.

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

PMDA considers as follows:

The results of pharmacokinetic studies of turoctocog alfa show similarity between turoctocog alfa and Advate, a FVIII product approved in Japan, in terms of pharmacokinetics. Since turoctocog alfa is a recombinant protein product, additional animal studies on the metabolism and excretion of the drug are not necessary in light of the guidance "Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals" (PFSB/ELD Notification No. 0323-1 dated March 23, 2012), and pharmacokinetic data limited to the absorption and distribution of turoctocog alfa are acceptable. The distribution of turoctocog alfa was investigated only for the first 90 minutes after administration, but no additional animal studies are necessary to evaluate the distribution of the drug beyond the first 90 minutes because the studies using ¹²⁵I-turoctocog alfa did not suggest the accumulation of the drug in particular tissues, along with the explanation provided by the applicant.

3.(iii) Summary of toxicology studies

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

Repeat dose toxicity studies and local tolerance studies were conducted to investigate the toxicity of turoctocog alfa.

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

Acute toxicity of turoctocog alfa was assessed after the first dose of the drug in the repeat dose toxicity studies. No deaths were observed after the first dose of turoctocog alfa in the repeat dose toxicity studies. The approximate lethal intravenous dose was determined to be >1250 IU/kg/day in rats and >5000 IU/kg/day in cynomolgus monkey.

3.(iii).A.(2) Repeat dose toxicity (4.2.3.2.1, 4.2.3.2.2)

Repeat dose toxicity studies were conducted in rats and cynomolgus monkeys.

In the repeat dose toxicity study, rats received the vehicle (n = 13/sex in the 0 IU/kg/day group) or turoctocog alfa at dose of 50, 250, or 1250 IU/kg/day (n = 19/sex/group) intravenously for 14 days. As a result, no findings indicating systemic toxicity or local reactions were observed, and all doses were well tolerated. Almost all animals in all turoctocog alfa dose groups developed neutralizing antibodies, which resulted in a decrease in exposure on Day 8 and thereafter and prolongation of APTT in the washout period in animals in the highest dose group. The no observed adverse effect level (NOAEL) for non-immunogenic toxicity was identified to be 1250 IU/kg/day.

In the repeat dose toxicity study in cynomolgus monkeys in which the vehicle (n = 5 male in the 0 IU/kg/day group), or 50, 1000, or 5000 IU/kg/day of turoctocog alfa (n = 8 males/group) were administered intravenously for 14 days, no findings indicating systemic toxicity or local reactions were observed, and all doses were well tolerated. Neutralizing antibodies developed in 18 of the 24 animals receiving turoctocog alfa. As a result, exposure to turoctocog alfa decreased on Day 14, and APTT values increased from Day 10 to Day 14 in animals with neutralizing antibodies. Histopathological examination revealed an enhanced bleeding tendency in all turoctocog alfa dose groups, which may reflect the development of anti-turoctocog alfa neutralizing antibodies that are cross-reactive to intrinsic FVIII. One animal receiving turoctocog alfa was euthanized due to the development of acquired haemophilia during the recovery period. The non-immunogenic NOAEL was identified to be 5000 IU/kg/day.

3.(iii).A.(3) Genotoxicity

No genotoxicity studies were conducted.

3.(iii).A.(4) Carcinogenicity

No carcinogenicity studies were conducted.

3.(iii).A.(5) Reproductive and developmental toxicity

No reproductive and developmental toxicity studies were conducted.

3.(iii).A.(6) Local tolerance (4.2.3.6.1)

A single dose of 0.15 mL of 500 IU/mL turoctocog alfa solution was administered to rabbits (n = 4 males/group) intravenously, or perivenously or intra-arterially (as erroneous injections) to assess injection site reactions. No animals showed significant local reactions.

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

PMDA considers the omission of genotoxicity and carcinogenicity studies is justified because turoctocog alfa is a recombinant plasma protein or a recombinant FVIII, in which the B-domain of

wild-type FVIII is truncated, and is activated in the body by thrombin to become structurally similar to intrinsic FVIIIa.

Regarding the fact that reproductive and developmental toxicity studies have not been performed with turoctocog alfa, the applicant discussed as follows:

No effects on the reproductive organs were observed in female rats in the repeat dose toxicity studies. No adverse events on fertility have been reported in association with the use of plasma-derived or recombinant FVIII products in the clinical setting.

PMDA considers as follows: No reproductive or developmental toxicity studies have been conducted for FVIII products approved in Japan (Advate and Kogenate). In the U.S., these products are rated Pregnancy Category C (animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks). As it is known that hypercoagulation due to blood coagulation factor XII deficiency or other causes is a risk factor for infertility (*Obstetrics & Gynecology*. 2007;109: 1146-55), and it is predictable that hypercoagulation due to overdose of turoctocog alfa causes toxicity during ontogeny, PMDA has concluded that the omission of reproductive and developmental toxicity studies is justified. Although the reproductive and developmental toxicity of turoctocog alfa at the recommended clinical dose was not assessed on the basis of non-clinical study data, the risk of reproductive and developmental toxicity should be low in humans receiving the drug at the recommended clinical dose, according to clinical experiences with conventional FVIII products. Accordingly, a caution should be given for turoctocog alfa similarly to conventional FVIII products to ensure that physicians administer the product to pregnant women or women who may be pregnant only if the potential benefits of the treatment outweigh the risks.

On the basis of the findings obtained in the toxicity studies of turoctocog alfa, PMDA has concluded that there are no specific concerns about systemic toxicity and local tolerance.

4. Clinical data

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

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

4.(i).A.(1) Analytical methods

The activity of FVIII in plasma was determined using the one-stage clotting assay and a two-stage chromogenic assay. The lower limit of quantification was 0.0125 international unit (IU)/mL in both assays. The concentration of FVIII inhibitors was determined using the Nijmegen modification of the Bethesda assay. The lower limit of quantification was 0.5 Bethesda unit (BU)/mL. As turoctocog alfa (genetical recombination) (referred to as "turoctocog alfa" hereinafter) is expected to be administered intravenously in the clinical setting, bioavailability and bioequivalence studies were not conducted.

4.(i).A.(2) Comparison of activity assays

It has been reported that when the FVIII activity of recombinant FVIII products is determined, the chromogenic assay tends to yield higher values than the one-stage clotting assay, and that the discrepancy between the 2 methods is 20% to 50% when the FVIII activity of other B-domain truncated recombinant FVIII products is determined (*Semin Thromb Hemost.* 2002;28:247-56).

In order to compare FVIII activity of turoctocog alfa determined with different methods in different institutions, a field study was conducted using turoctocog alfa and the full-length recombinant FVIII product Advate. The FVIII activity of plasma samples derived from patients with severe haemophilia A and spiked with turoctocog alfa or Advate to final concentrations of 0.03, 0.2, 0.6, or 0.9 IU/mL was determined in a total of 36 institutions, of which 33 used the one-stage clotting assay and 5 used the chromogenic assay (2 institutions used both assays). The applicant described the results as follows:

For both turoctocog alfa and Advate, the one-stage clotting assay tended to yield values lower than the target values at higher concentrations, and values higher than target values at lower concentrations. The chromogenic assay yielded values higher than target values for both turoctocog alfa and Advate at all concentrations tested. Although the FVIII activity of turoctocog alfa was generally higher than that of Advate, the difference between the 2 products was about 10% and was not considered clinically relevant. Although the 2 assays yielded different results, both turoctocog alfa and Advate showed a tendency toward higher chromogenic/one-stage clotting assay result ratio at higher concentrations (Table 4-1). The intra- and inter-institutional coefficients of variation of the 2 assays were similar between turoctocog alfa and Advate. The applicant considered that the FVIII activity of turoctocog alfa in plasma samples could be determined reliably as in the case of the full-length recombinant FVIII product Advate, and the use of reference standards to standardize the 2 assays is not necessary.

Table 4-1. Chromogenic/one-stage clotting assay result ratio

	Turoctocog alfa				Advate				Standard sample ¹
Target FVIII concentration (IU/mL)	0.03	0.2	0.6	0.9	0.03	0.2	0.6	0.9	0.8
Chromogenic/one-stage clotting assay result ratio	0.68	1.01	1.23	1.30	0.66	0.90	1.12	1.19	0.99

1: Plasma sample provided by the Scientific and Standardization Committee (SSC) of the International Society on Thrombus and Haemostasis (ISTH)

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

The field survey in medical institutions revealed that there were differences between FVIII activity values by the one-stage clotting assay and those by the chromogenic assay. PMDA requested the applicant to discuss potential problems caused by using different FVIII activity assays in different institutions in the treatment with turoctocog alfa in the clinical setting.

The applicant responded as follows:

Since the target trough level of FXIII activity for FVIII replacement therapy in patients with severe haemophilia is as low as 1% to 2% of normal (*Haemophilia*. 2013;19:e1-47), it is unlikely that differences in FVIII activity values obtained with different methods will affect the dose of turoctocog alfa selected for patients. As measured trough values vary substantially, physicians select the dose of turoctocog alfa based on not only that measured trough concentrations but also estimated trough concentration calculated using FVIII recovery and half-life as well as clinical conditions such as frequency of bleeds, complications, and physical activity level. Usually, as patients tend to visit the same institution and are tested with the same assay to determine FVIII activity, the difference in FVIII activity measurement between the 2 assays may not affect the assessment of FVIII activity in individual patients in the clinical setting. Based on the above considerations, the applicant considered that using different FVIII activity assays does not cause any clinically significant problems.

PMDA accepted the applicant's response.

4.(ii) Summary of clinical pharmacology studies

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

As the evaluation data for clinical pharmacology, the applicant submitted the results of a foreign phase I study (5.3.3.5.1. Study NN7008-3522), a foreign pharmacokinetic study (5.3.3.5.3. Study NN7008-3893), a global phase III study (5.3.5.2.1. Study NN7008-3543), and a pharmacokinetic study in Japan (5.3.3.5.2. Study NN7008-3600) in patients with haemophilia A, as well as a foreign phase III study in children with haemophilia A (5.3.5.2.2. Study NN7008-3545). Values are expressed as mean \pm standard deviation (SD) unless otherwise indicated. The above series of clinical studies (Study NN7008-XXXX) are expressed as Trial XXXX hereinafter.

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

No studies using human biomaterials were conducted.

4.(ii).A.(2) Studies in healthy adults

No studies in healthy adults were conducted.

4.(ii).A.(3) Adult patients

4.(ii).A.(3).1 Foreign phase I study (5.3.3.5.1: Study NN7008-3522, From March 2009 to October 2009)

A total of 23 patients with severe haemophilia A (FVIII \leq 1%) who were 12 to 55 years of age and who had been previously treated with other FVIII products for at least 150 days received a single intravenous dose of Advate at 50 IU/kg with a washout period of 4 days, followed by an intravenous dose of turoctocog alfa at 50 IU/kg. Plasma FVIII activity was determined at pre-dose and at 15 and 30 minutes, 1, 4, 8, 12, 24, 30, and 48 hours post-dose using the one-stage clotting assay and the chromogenic assay. After the exclusion of 3 patients with outlying values, FVIII activity data adjusted for actual dose and strength of the drug in the vial were used to calculate pharmacokinetic parameters

of turoctocog alfa (Table 4-2). No results of the chromogenic assay were reported for the 3 patients with outliers.

Table 4-2. Single intravenous dose pharmacokinetics of turoctocog alfa (full analysis set, mean \pm SD)

	One-stage clotting assay (N = 20)	Chromogenic assay (N = 20)
AUC (h·IU/mL)	14.22 \pm 13.75	18.70 \pm 5.08
FVIII recovery (IU/mL/IU/kg)	0.020 \pm 0.002 ¹	0.028 \pm 0.006
t _{1/2} (h)	10.83 \pm 4.95	10.04 \pm 3.59 ²
CL (mL/h/kg)	3.74 \pm 0.95	2.87 \pm 0.80

N : Number of patients

1 : Data of a patient in whom FVIII activity at 30 minutes was lower than that at 1 hour after administration were excluded from the calculation of FVIII recovery.

2 : The t_{1/2} from 1 patient has been excluded as it was considered an outlying value (48.5 hours).

When the one-stage clotting assay was used, the 90% confidence interval for the Advate-to-turoctocog alfa ratios of geometric mean pharmacokinetic parameters were within the predefined acceptable range of bioequivalence (0.8-1.25) (Table 4-3). For the chromogenic assay, the FVIII activity of turoctocog alfa was higher than that of Advate, and the 90% confidence interval for the Advate-to-turoctocog alfa ratios of geometric mean pharmacokinetic parameters were outside the acceptable range of bioequivalence (Table 4-3). The applicant explained that the difference between turoctocog alfa and Advate in FVIII activity determined by the chromogenic assay showed a tendency similar to that observed in the field study, and that the pharmacokinetic profile of a single intravenous dose of turoctocog alfa was similar to that of Advate.

Table 4-3. Advate-to-turoctocog alfa ratios of geometric mean pharmacokinetic parameters and 90% confidence interval (CI) (full analysis set)

	One-stage clotting assay (Advate N = 23, turoctocog alfa N = 20)	Chromogenic assay (Advate N = 20, turoctocog alfa N = 20)
AUC (h·IU/mL)	0.917 [0.860, 0.978]	0.800 [0.765, 0.836]
FVIII recovery (IU/mL/IU/kg)	0.921 ¹ [0.859, 0.987]	0.824 [0.773, 0.878]
t _{1/2} (h)	1.070 [0.981, 1.168]	1.211 ² [1.140, 1.287]
CL (mL/h/kg)	1.091 [1.023, 1.163]	1.251 [1.197, 1.307]

N : Number of patients

1 : Data of 1 patient in whom FVIII activity at 30 minutes was lower than that at 1 hour after administration were excluded from the calculation of FVIII recovery.

2 : The t_{1/2} from 1 patient has been excluded as it was considered an outlying value (48.5 hours).

4.(ii).A.(3).2) Global phase III study (5.3.5.2.1. Study NN7008-3543, From April 2009 to September 2011)

The pharmacokinetic part of this study included 22 non-Japanese patients with severe haemophilia A (FVIII \leq 1%), who were 12-56 years of age and who completed Trial 3522. The patients received a single intravenous dose of turoctocog alfa at 50 IU/kg, after preventive dosing of turoctocog alfa for 3 to 6 months at 20 to 40 IU/kg every second day or 20 to 50 IU/kg 3 times a week with a washout period of 4 days. FVIII activity was determined at pre-dose and at 15 and 30 minutes, 1, 4, 8, 12, 24, 30, and 48 hours post-dose. After the data from 7 patients who had outlying values in Trial 3522 or

3543 were excluded, FVIII activity data adjusted for actual dose were used to calculate pharmacokinetic parameters, and a comparison of these parameters was made between Trials 3543 and 3522 (Table 4-4). The applicant explained that the pharmacokinetic profile of a single dose of turoctocog alfa after 3-6 months of continuous dosing in Trial 3543 were comparable to that of the first dose of the drug in Trial 3522.

Table 4-4. Pharmacokinetic parameters of turoctocog alfa following the first dose (Trial 3522) and following a single dose after 3- to 6-month preventive dosing (Trial 3543) (Full analysis set, mean ± SD)

	One-stage clotting assay		Chromogenic assay	
	Trial 3522 (N = 15)	Trial 3543 (N = 15)	Trial 3522 (N = 15)	Trial 3543 (N = 15)
AUC (h·IU/mL)	13.87 ± 2.68	13.90 ± 3.63	17.65 ± 3.55	16.93 ± 5.26
FVIII recovery (IU/mL/IU/kg)	0.020 ± 0.002	0.023 ± 0.003	0.027 ± 0.005	0.028 ± 0.004
t _{1/2} (h)	10.47 ± 2.34	10.50 ± 5.19	9.47 ± 2.38 ¹	8.65 ± 2.09
Total CL (mL/h)	269.7 ± 75.57	284.4 ± 91.82	213.0 ± 57.99	238.9 ± 84.64

Total CL: total clearance

N: number of patients

1: The t_{1/2} from 1 patient has been excluded as it was considered to be an outlier (48.5 hours).

4.(ii).A.(3).3 Foreign pharmacokinetic study (5.3.3.5.3: Study NN7008-3893, from June 2011 to September 2011)

Four non-Japanese patients aged 12 to 56 years who completed Trial 3543 received single intravenous doses of turoctocog alfa from 2 different lots at 50 ± 5 IU/kg with a washout period of 4 days between doses. FVIII activity was determined at pre-dose and at 15 and 30 minutes, 1, 4, 8, 12, 24, 30, and 48 hours post-dose, and FVIII activity data adjusted for actual dose were used to calculate pharmacokinetic parameters. Pharmacokinetic parameters obtained with the one-stage clotting assay and the chromogenic assay were as follows: was 16.68 ± 3.26 and 24.71 ± 6.26 h·IU/mL for the area under the activity versus time curve from zero hours to infinity (AUC_{0-∞}), respectively; 0.024 ± 0.007 and 0.031 ± 0.009 IU/mL/IU/kg for FVIII recovery, respectively; 11.16 ± 2.79 and 13.00 ± 2.44h for terminal half-life (t_{1/2}), respectively; and 3.08 ± 0.56 and 2.10 ± 0.43mL/h/kg for total body clearance (CL) normalized for body weight, respectively. Pharmacokinetic parameters in Trial 3893 were different from those in Trial 3522 (Table 4-2). The applicant explained that the difference in pharmacokinetic parameters between Trials 3893 and 3522 is partly attributable to the difference in age of study subjects (mean age was 33 years and 24 years, respectively). Trial 3893 was conducted in patients who completed Trial 3543, and Trial 3543 included patients who completed Trial 3522. There was no overlap between the groups of patients enrolled in Trials 3893 and 3522.

4.(ii).A.(3).4 Pharmacokinetic study in Japan (5.3.3.5.2: Study NN7008-3600, from November 2010 to October 2011)

Six patients who completed Trial 3543 received a single intravenous dose of turoctocog alfa at 50 ± 5 IU/kg. FVIII activity was determined at pre-dose and at 15 and 30 minutes, 1, 4, 8, 12, 24, 30, and 48 hours post-dose, and FVIII activity data adjusted for actual dose were used to calculate

pharmacokinetic parameters. Pharmacokinetic parameters obtained with the one-stage clotting assay and the chromogenic assay were as follows: was 23.14 ± 10.81 and 29.40 ± 13.23 h·IU/mL for AUC, respectively; 0.024 ± 0.005 and 0.033 ± 0.007 IU/mL/IU/kg for FVIII recovery, respectively; 12.61 ± 5.07 and 15.46 ± 6.76 h for $t_{1/2}$, respectively; and 2.54 ± 1.06 and 1.93 ± 0.64 mL/h/kg for CL, respectively. Mean FVIII recovery and AUC in Trial 3600 were higher than those in Trial 3522 (Table 4-2), and mean $t_{1/2}$ in Trial 3600 was longer than that in Trial 3522 (Table 4-2). The applicant explained that the difference in pharmacokinetic parameters was attributable to the difference in mean age of participants in Trials 3600 and 3522 (33 years and 24 years, respectively). Trial 3600 was conducted in patients who completed Trial 3543, and Trial 3543 included patients who completed Trial 3522. There was no overlap between the groups of patients enrolled in Trials 3600 and 3522.

4.(ii).A.(4) Pediatric patients

4.(ii).A.(4).1) Foreign phase III study (5.3.5.2.2: Study NN7008-3545, from June 2010 to November 2011)

A total of 28 non-Japanese children (0 to <12 years of age) with severe haemophilia A (FVIII $\leq 1\%$) who had been previously treated with a FVIII product for at least 50 days received a single intravenous dose of turoctocog alfa at 50 ± 5 IU/kg, and plasma FVIII activity was determined at pre-dose and at 30 minutes, 1, 4, 10, 24, and 48 hours post-dose. Before the administration of turoctocog alfa, 26 of the 28 patients received a single intravenous injection of the previously-used FVIII product at 50 ± 5 IU/kg, and plasma FVIII activity was determined at pre-dose and at 30 minutes, 10, 24, and 32 hours post dose. For the subgroup of children aged 0 to <6 years and those aged 6 to <12 years, FVIII activity adjusted for actual dose was used to calculate pharmacokinetic parameters. The applicant described the results as follows: Pharmacokinetic parameters in children aged 0 to <6 years were similar to those in children aged 6 to <12 years (Table 4-5). As compared with the results in Trial 3522 in patients aged ≥ 12 years (Table 4-2), mean AUC was lower in patients aged <12 years than in those aged ≥ 12 years, and mean CL was higher in patients aged <12 years than in those aged ≥ 12 years. Mean $t_{1/2}$ was shorter in patients aged <12 years than in those aged ≥ 12 years. Change over time in plasma FVIII activity after the single administration of the previously used FVIII product was similar to that of turoctocog alfa, and the applicant explained that turoctocog alfa and the previously used FVIII product showed a similar pharmacokinetic profile.

Table 4-5. Pharmacokinetic parameters in children with haemophilia (full analysis set, mean \pm SD)

	One-stage clotting assay		Chromogenic assay	
	0-<6 years of age (N = 14)	6-<12 years of age (N = 14)	0-<6 years of age (N = 14)	6-<12 years of age (N = 14)
AUC (h·IU/mL)	9.89 \pm 4.14	11.09 \pm 3.73	12.21 \pm 4.38	14.36 \pm 3.48
FVIII recovery (IU/mL/IU/kg)	0.018 \pm 0.007	0.020 \pm 0.004	0.022 \pm 0.006	0.025 \pm 0.006
$t_{1/2}$ (h)	7.65 \pm 1.84	8.02 \pm 1.89	9.99 \pm 1.71	9.42 \pm 1.52
CL (mL/h/kg)	6.26 \pm 3.73	5.02 \pm 1.67	4.60 \pm 1.75	3.70 \pm 1.00

N: the number of patients

4.(ii).A.(5) Drug interactions

No studies on drug interactions were conducted.

4.(ii).A.(6) Pharmacodynamic studies

No pharmacodynamic studies were conducted.

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

4.(ii).B.1 Comparison of pharmacokinetics between turoctocog alfa and Advate

Table 4-6 shows the Advate-to-turoctocog alfa ratios of geometric means of pharmacokinetic parameters in patients including outliers and their 90% confidence interval in Trial 3522. Similar to the pharmacokinetic data obtained from patients excluding outliers (Table 4-3), the 90% confidence interval for the Advate-to-turoctocog alfa ratios of the geometric means of pharmacokinetic parameters were within the predefined acceptable range of bioequivalence (0.8-1.25) when the one-stage clotting assay was used, but were outside the range when the chromogenic assay was used.

Table 4-6. Advate-to-turoctocog alfa ratios of geometric mean pharmacokinetic parameters and 90% confidence interval (full analysis set)

	One-stage clotting assay (N=23)	Chromogenic assay (N=20)
AUC (h·IU/mL)	0.929 [0.871, 0.990]	0.800 [0.765, 0.836]
FVIII recovery (IU/mL/IU/kg)	0.999 [0.905, 1.102]	0.824 [0.773, 0.878]
t _{1/2} (h)	1.071 [0.988, 1.161]	1.107 [0.937, 1.308]
CL (mL/h/kg)	1.077 [1.010, 1.148]	1.251 [1.197, 1.307]

N: number of patients

PMDA has concluded that the pharmacokinetic profiles of turoctocog alfa and Advate have no substantial differences that may affect the efficacy and safety of turoctocog alfa in the clinical setting for the following reasons: In Trial 3522, the confidence interval for the Advate-to-turoctocog alfa ratios of pharmacokinetic parameters were within the predefined acceptable range, although that for one parameter did not include 1.0, when the one-stage clotting assay was used, while they did exceed the range when the chromogenic assay was used.

4.(ii).B.2 Age and pharmacokinetics

The applicant explained the effect of age on the pharmacokinetics of turoctocog alfa as follows: Using the results of Trials 3522, 3545, 3893, and 3600, the applicant plotted pharmacokinetic parameters (FVIII recovery, AUC, and t_{1/2}) over age to assess the relationship between age and pharmacokinetic parameters of turoctocog alfa. AUC and t_{1/2} tended to increase as age increased, while no clear relationship was observed between FVIII recovery and age. In other FVIII products, some pharmacokinetic parameters have been reported to correlate with age (*Blood*. 2012;119:612-18).

PMDA considers as follows:

Age-related differences in pharmacokinetic parameters are not likely to be clinically relevant for the following reasons: (1) although some pharmacokinetic parameters tend to show age-related changes, physicians determine the dose of turoctocog alfa according to the location and severity of bleeding as well as clinical status of individual patients; and (2) the applicant explained that the pharmacokinetic profile of turoctocog alfa was similar to that of the FVIII products which were used previously by the participants in Trial 3545.

4.(iii) Summary of clinical efficacy and safety

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

As the data for evaluation of efficacy and safety, the applicant submitted the results of a foreign phase I study, a pharmacokinetic study in Japan, a foreign pharmacokinetic study, 2 global phase III studies, and a foreign phase III study.

Table 4-7. List of clinical studies on the efficacy and safety of turoctocog alfa

Category of data	Site	Title	Phase	Participants	No. of patients receiving the drug	Dosage regimens
Evaluation data	Outside Japan	NN7008-3522	I	Patients with severe haemophilia A (12-55 years of age)	23	After a single dose of Advate at 50 IU/kg, a single dose of turoctocog alfa at 50 IU/kg was given.
	Japan	NN7008-3600	—	Patients with severe haemophilia A (12-65 years of age)	7	A single dose of turoctocog alfa at 50 IU/kg.
	Outside Japan	NN7008-3893	—	Patients with severe haemophilia A (12-56 years of age)	4	A single dose of turoctocog alfa at 50 IU/kg
	Global	NN7008-3543	III	Patients with severe haemophilia A (12-65 years of age)	150 (9 patients in Part C)	Prophylaxis: 20-40 IU/kg every second day or 20-50 IU/kg 3 times weekly. Treatment of bleeds: At the investigator's discretion, administer the drug to aim at a plasma FVIII activity of at least 0.50 IU/mL. Use in patients undergoing surgery (Part C): From the day of surgery (Day 1) to Day 6 ("Day 6" was changed to "Day 7" during the study), turoctocog alfa was administered to aim at a plasma FVIII trough level or steady-state FVIII concentration (changed during the study to delete "or steady-state FVIII concentration") of >0.50 IU/mL. From Day 7 to Day 10 [changed to "from Day 8 to the day of returning to preventive treatment (including both prevention and treatment of bleeds)"], the dose was adjusted at the investigator's discretion.
	Outside Japan	NN7008-3545	III	Patients with severe haemophilia A (<12 years of age)	63	Prophylaxis: 25-50 IU/kg every second day or 25-60 IU/kg 3 times weekly. Treatment of bleeds: At the investigator's discretion, administer the drug to aim at a plasma FVIII activity of at least 0.50 IU/mL.
	Global	NN7008-3568	III	Patients with severe haemophilia A (0-65 years of age)	55 patients under 12 and 132 patients over 12 years of age. (Cut-off date: November 21, 2011)	Prophylaxis: 20-50 IU/kg every second day or 20-60 IU/kg 3 times weekly. Treatment of bleeds: At the investigator's discretion, administer the drug to aim at a plasma FVIII activity of at least 0.50 IU/mL. Use in patients undergoing surgery: From the day of surgery (Day 1) to Day 7, turoctocog alfa was administered to aim at a plasma FVIII trough level or steady-state FVIII concentration of >0.50 IU/mL. From Day 8 to the day of returning to preventive treatment (including both prevention and treatment of bleeds), the dose was adjusted at the investigator's discretion.

An outline of each clinical study is as follows. Clinical studies (Study NN7008-XXXX) are expressed as Trial XXXX hereinafter.

4.(iii).A.(1) Phase I studies and pharmacokinetic studies

4.(iii).A.(1).1) Foreign phase I study (5.3.3.5-1: Study NN7008-3522, from March 2009 to October 2009)

A multicenter, open-label, non-controlled clinical study in 6 institutions outside Japan was conducted to compare the pharmacokinetics of turoctocog alfa and Advate in patients with severe haemophilia A (FVIII \leq 1%) (12 to 55 years of age), who have a history of treatment with FVIII products for at least 150 days, and who have no detectable FVIII inhibitors. The target sample size was 23 patients.

Patients received a single dose of Advate at 50 IU/kg with a washout period of 4 days, followed by a single dose of turoctocog alfa at 50 IU/kg.

The results of pharmacokinetic analysis are described in the section "4.(ii).A.(3).1) Foreign phase I study."

All 23 patients who participated and received the study drugs in the study were included in the full analysis set, and were evaluated for safety.

Of the 23 patients, 8 patients (34.8%) experienced at least 1 adverse event during the study. Four of the 23 patients (17.4%) had at least 1 adverse event for which a causal relationship with the drug could not be excluded (defined as an "adverse drug reaction").

Table 4-8. Adverse events and adverse drug reactions reported during the study period (n = 23, full analysis set)

	Adverse events			Adverse drug reactions		
	Advate n (%)	Turoctocog alfa n (%)	Total n (%)	Advate n (%)	Turoctocog alfa n (%)	Total n (%)
Incorrect dose administered	2 (8.7)	5 (21.7)	6 ¹ (26.1)	0 (0)	0 (0)	0 (0)
Sunburn	1 (4.3)	0 (0)	1 (4.3)	0 (0)	0 (0)	0 (0)
Injection site erythema	1 (4.3)	3 (13.0)	4 (17.4)	1 (4.3)	3 (13.0)	4 (17.4)
Injection site pain	1 (4.3)	0 (0)	1 (4.3)	1 (4.3)	0 (0)	1 (4.3)
Injection site swelling	1 (4.3)	0 (0)	1 (4.3)	1 (4.3)	0 (0)	1 (4.3)
Pyrexia	0 (0)	1 (4.3)	1 (4.3)	0 (0)	1 (4.3)	1 (4.3)
Palpitations	0 (0)	1 (4.3)	1 (4.3)	0 (0)	0 (0)	0 (0)
Hematocrit decreased	0 (0)	1 (4.3)	1 (4.3)	0 (0)	0 (0)	0 (0)
Hemoglobin decreased	0 (0)	1 (4.3)	1 (4.3)	0 (0)	0 (0)	0 (0)
Red blood cell count decreased	0 (0)	1 (4.3)	1 (4.3)	0 (0)	0 (0)	0 (0)
Headache	1 (4.3)	0 (0)	1 (4.3)	0 (0)	0 (0)	0 (0)

N: number of patients

n: number of patients with any adverse event

1 : One patient received Advate and turoctocog alfa at incorrect doses.

There were no deaths or serious adverse events reported in this study.

4.(iii).A.(1).2) Pharmacokinetic study in Japan 5.3.3.5-2: Study NN7008-3600, from November 2010 to October 2011)

A multicenter, open-label, non-controlled clinical study was conducted in 6 institutions in Japan to investigate the pharmacokinetics of a single intravenous dose of turoctocog alfa in patients who completed Trial 3543. The target sample size was 6 patients.

Following preventing dosing (including both prevention and treatment of bleeds) as did in Trial 3543, a single dose of turoctocog alfa at 50 ± 5 IU/kg was administered intravenously after a washout period of 4 days.

The results of pharmacokinetic analysis in this study are described in the section "4.(ii).A.(3).4) pharmacokinetics study in Japan."

All 7 patients who participated in the study were included in the full analysis set and the safety analysis set.

Of the 7 patients, 3 patients (42.9%) experienced at least 1 adverse event during the study. The adverse events reported were diarrhoea, stomatitis, and dermatitis allergic, all of which occurred in 1 patient each. All these events were mild in severity, and were not related to the study drug. There were no deaths or serious adverse events reported during this study period.

4.(iii).A.(1).3) Foreign pharmacokinetic study (5.3.3.5-3: Study NN7008-3893, from June 2011 to September 2011)

A randomized, open-label study was conducted in 2 institutions outside Japan to evaluate the pharmacokinetics of single intravenous doses of 2 different lots of turoctocog alfa in patients aged 12 to 56 years who completed Trial 3543. The target sample size was 4 patients.

Following preventing dosing (including both prevention and treatment of bleeds) as did in Trial 3543, patients received a single dose using either one of the 2 lots of turoctocog alfa at 50 ± 5 IU/kg with a washout period of 4 days, followed by the other dose).

The results of pharmacokinetic analysis are described in the item "4.(ii).A.(3).3) Foreign pharmacokinetic study."

All 4 patients who participated in the study were included in the full analysis set and the safety analysis set.

Of the 4 patients, 2 patients (50.0%) experienced at least 1 adverse event during the study. The adverse events reported were abdominal discomfort and hyperglycaemia, both of which occurred in 1 patient

each. These events were mild in severity and considered not related to the study drug. There were no deaths or serious adverse events reported in this study.

4.(iii).A.(2) Phase III studies

4.(iii).A.(2).1) Global phase III study (5.3.5.2.1 : Study NN7008-3543, from April 2009 to September 2011)

A global open-label non-controlled study was conducted in 48 institutions in 15 countries including Japan in order to evaluate the safety and efficacy of turoctocog alfa in prevention and treatment of bleeds in patients with severe haemophilia A (FVIII \leq 1%) (12 to 65 years of age) who had been treated with other FVIII products for at least 150 days. The target sample size was 140 patients.

This study consisted of the following three parts:

Part A including patients who completed Trial 3522 Part B including patients who participated in this study and who did not participate in Trial 3522

Part C including patients from Part A or B undergoing surgical procedure that requires at least 7 consecutive days of FVIII treatment

In Parts A and B, turoctocog alfa was administered as the preventive treatment at 20 to 40 IU/kg every second day or 20 to 50 IU/kg 3 times weekly for at least 75 preventive exposure days (excluding days for treatment of bleeds) to achieve a trough level of \geq 0.01 IU/mL for prevention of bleeds. The dose for treatment of bleeds was adjusted to achieve a post-injection level of at least 0.50 IU/mL of plasma FVIII activity. For the treatment of a severe bleeding episode, higher doses up to a total dose of 100 IU/kg per day could be used at the investigator's discretion for up to 14 days (the dose was changed to "200 IU/kg per day" during the study). In Part C, from the day of surgery (Day 1) to Day 6 (which was changed to "Day 7" during the study), turoctocog alfa was administered to aim at a plasma FVIII trough level or steady-state FVIII concentration (which was changed to "a plasma FVIII trough level" during the study) of $>$ 0.50 IU/mL. From Day 7 to Day 10 (which was changed to "from Day 8 to the day of returning to preventive treatment [including both prevention and treatment of bleeds]"), the dose was adjusted at the investigator's discretion. In Part A, the pharmacokinetic part of Trial 3543, the pharmacokinetic profile was evaluated after a single injection of turoctocog alfa at 50 IU/kg after 3 to 6 months of preventive dosing with the drug (including both prevention and treatment of bleeds) with a washout period of at least 4 days. The results of pharmacokinetic evaluation are described in the section "4.(ii).A.(3).2) Global phase III clinical study."

Trial 3543 enrolled 150 patients (22 patients in Part A, 128 patients in Part B, and 9 patients, who had enrolled in Part A or B, in Part C). All 150 patients were included in the full analysis set and the safety analysis set.

The number of per-patient exposure days with turoctocog alfa was 84.6 ± 14.1 days (mean \pm SD; range 11-172 days).

The primary endpoint of the study was to assess the efficacy of turoctocog alfa in treatment and prevention of bleeds in a descriptive manner. However, during the study period, the primary endpoint was changed to the incidence rate of FVIII inhibitors (calculated as the percentage of patients with FVIII inhibitors [≥ 0.6 BU/mL] among patients with at least 50 exposure days plus those developing FVIII inhibitors with < 50 exposure days) after consultation with the Food and Drug Administration (FDA) of the U.S. The change of the primary endpoint did not require a change in the target sample size.

The incidence rate of FVIII inhibitors, the primary endpoint, was 0%, and the upper one-sided 97.5% confidence limit was 2.46%, which was below the target value (6.8%) that was pre-defined based on the FDA’s recommendation, which states that an occurrence of FVIII inhibitors in ≤ 1 patient in a clinical study enrolling 80 patients is clinically acceptable.

The secondary endpoints of the study included the efficacy of turoctocog alfa in preventing and treating bleeds, which was evaluated on the basis of the estimated annualized bleeding rate for prevention and a predefined 4-point scale (Table 4-9) for treatment.

Table 4-9. Definition of haemostatic response (acute bleeds)

Excellent	Abrupt pain relief and/or unequivocal improvement in objective signs of bleeding within approximately 8 hours after a single infusion
Good	Definite pain relief and/or improvement in signs of bleeding within approximately 8 hours after an infusion, but possibly requiring more than one infusion for complete resolution
Moderate	Probable or slight beneficial effect within approximately 8 hours after the first infusion; usually requiring more than one infusion
None	No improvement, or worsening of symptoms

In Part C, haemostatic response during and after surgery was evaluated using a predefined 4-point scale (Table 4-10).

Table 4-10. Definition of haemostatic response during and after surgery

During surgery	Excellent	Blood loss less than expected in this type of patient and procedure
	Good	Blood loss as expected
	Moderate	Blood loss more than expected
	None	Uncontrolled bleeding
After surgery	Excellent	Good or better than expected in this type of patient and procedure
	Good	Minimal negative impact on quality of haemostasis
	Moderate	Less than optimal for the type of procedure, maintained without change of treatment regimen
	None	Bleeding due to inadequate therapeutic response with adequate dosing; change of regimen required

A total of 499 bleeds were treated during the study. The estimated annualized bleeding rate was 6.50 bleeds/patient/year (95% CI, 5.30-7.97). The success rate for treatment of bleeds (percentage of bleeds for which haemostatic response was rated as excellent or good) was 80.8% (403 of 499 bleeds). In Part C, a total of 9 surgeries in 9 patients were performed during the study. Eight of these were major surgeries (arthropathy for 4 patients, arthropathy and chronic pain in the left knee for 1 patient, synovitis for 1 patient, circumcision for 1 patient, recurrent hemarthrosis for 1 patient), and 1 was a

minor surgery (removal of semi-impacted tooth and tooth root for 1 patient). Haemostasis was successful (haemostatic effect was rated as excellent or good) in 9 of the 9 patients who received turoctocog alfa during or after surgery.

Since no Japanese patients were enrolled in Trial 3522, there were no Japanese patients in Part A. As no Japanese patients participating in Trial 3543 underwent surgery, there were no Japanese patients evaluated in Part C. Among Japanese patients enrolled in Part B, 9 patients were included in the full analysis set. Among the 9 Japanese patients, the incidence rate of FVIII inhibitors (≥ 0.6 BU/mL) was 0% (0 of 9 patients), and the upper one-sided 97.5% confidence limit was 33.6%. The Japanese patients had a total of 6 bleeds during the study period, and the estimated bleeding rate was 1.34 bleeds/patient/year (95% CI, 0.54-3.31). The success rate for treatment of bleeds (percentage of bleeds for which haemostatic response was rated as excellent or good) was 100% (6 of 6 bleeds).

Of the 150 patients enrolled in the study, 100 patients (66.7%) experienced at least 1 adverse event during the study period. Table 4-11 lists adverse events reported in $\geq 2.0\%$ of the patients.

Table 4-11. Adverse events reported in $\geq 2.0\%$ of the patients (safety analysis set)

	Part A and Part B (N = 150) n (%)	Part C (N = 9)* n (%)
Incorrect dose administered	15 (10.0)	0 (0.0)
Nasopharyngitis	12 (8.0)	0 (0.0)
Influenza	4 (2.7)	0 (0.0)
Upper respiratory tract infection	4 (2.7)	0 (0.0)
Pharyngitis	3 (2.0)	0 (0.0)
Sinusitis	3 (2.0)	0 (0.0)
Toothache	6 (4.0)	0 (0.0)
Abdominal pain upper	3 (2.0)	0 (0.0)
Headache	14 (9.3)	0 (0.0)
Pain in extremity	3 (2.0)	0 (0.0)
Arthralgia	3 (2.0)	0 (0.0)
Nasal congestion	5 (3.3)	0 (0.0)
Cough	3 (2.0)	0 (0.0)
Oropharyngeal pain	3 (2.0)	0 (0.0)
Pyrexia	6 (4.0)	0 (0.0)
Hepatic enzyme increased	3 (2.0)	0 (0.0)

N: number of participants

n: number of patients with any adverse event

* : Participants in Part C were included either Part A or Part B.

In Parts A and B, a total of 17 adverse events probably or possibly related to the study drug were reported in 11 patients (7.3%). The adverse events reported were incorrect dose administered (3 events), hepatic enzyme increased (2 events), and fatigue, feeling hot, pyrexia, heart rate increased, dizziness, headache, hypertension, lymphoedema, sinus tachycardia, musculoskeletal stiffness, insomnia, and rash (1 event each). One patient was withdrawn due to an adverse event of fatigue lasting for ≥ 24 hours after every infusion of turoctocog alfa. In Part C, no adverse events probably or possibly related to the study drug were reported.

During the study period, 9 serious adverse events were reported in 7 patients (4.7%). The serious adverse events reported were melaena (2 events), and hypertension, sinus tachycardia, insomnia, upper

gastrointestinal haemorrhage, hepatic enzyme increased, road traffic accident, and fall (accidental) (1 event each). No deaths were reported during the study.

Among the Japanese patients enrolled in the study (9 patients included in the safety analysis set), 18 adverse events were reported in 7 patients. No deaths or other serious adverse events were reported. Adverse events reported in Japanese patients were epigastric discomfort (3 events), nasopharyngitis (2 events), and headache, toothache, pharyngitis, sputum increased, injury, contusion, paronychia, dizziness, heart rate increased, lymphoedema, musculoskeletal stiffness, pain, and gastroenteritis (1 event each). The outcome of a patient with lymphoedema was reported as not recovered.

The applicant explained that there was no particular tendency in adverse event profile observed in Japanese patients as compared with the overall population.

4.(iii).A.(2).2 Study in children (5.3.5.2.2: Study NN7008-3545, from June 2010 to November 2011)

A multicenter, open-label, non-controlled clinical study in 39 institutions outside Japan was conducted to evaluate the safety, efficacy and pharmacokinetics of turoctocog alfa in patients with severe haemophilia A (FVIII \leq 1%) who were <12 years of age, and who had a history of treatment with FVIII products for at least 50 days, and no detectable FVIII inhibitors. The target sample size was 60 patients, and 26 institutions enrolled patients.

This study comprised a pharmacokinetic part and a clinical part. The pharmacokinetic part included 13 children aged 0 to <6 years and 13 children aged 6 to <12 years. Patients who were enrolled directly in the clinical part and patients who completed the pharmacokinetic part (including both patients for prevention and treatment of bleeds) underwent preventive treatment to be included in the safety and efficacy assessment.

For prevention of bleeds, patients received turoctocog alfa at 25 to 50 IU/kg every second day or 25 to 60 IU/kg 3 times weekly according to the plasma FVIII trough level at the investigator's discretion. In the case of acute bleeds, the dose for treatment of bleeds was adjusted to achieve a post-injection level of at least 0.50 IU/mL of plasma FVIII activity. For treatment of a severe bleed, doses up to 150 IU/kg per day could be used at the discretion of the investigator.

The results of pharmacokinetic analysis are described in the section "4.(ii).A.(4).1) Foreign phase III study."

In this study, a total of 65 patients were enrolled. The pharmacokinetic and clinical parts included 30 and 35 patients, respectively. Of the 65 patients enrolled in the study, 63 patients were included in the full analysis set, after exclusion of 2 patients who received conventional FVIII product only for

pharmacokinetic assessment in the pharmacokinetic part. The number of turoctocog alfa exposure days per patient was 60.0 ± 11.7 days (mean \pm SD), ranging from 20 to 104 days.

The primary endpoint of the study was the incidence rate of FVIII inhibitors (calculated as the percentage of patients with FVIII inhibitors (≥ 0.6 BU/mL) among patients with at least 50 exposure days plus those developing FVIII inhibitors with < 50 exposure days). The rate was 0% (0 of 59 patients), and the upper one-sided 97.5% confidence limit was 6.06%. The upper limit was below the target value (10.7%), which was set by the European Medicines Agency (EMA) as a clinically acceptable level. The figure is consistent with the criteria set up based on FDA's recommendation which states that an occurrence of FVIII inhibitors in ≤ 1 patient in a clinical study in children with a target sample size of 50 patients is acceptable.

The efficacy of turoctocog alfa in preventing and treating bleeds, secondary endpoints of the study, were evaluated on the basis of the estimated annualized bleeding rate for prevention and a predefined 4-point scale (Table 4-9) for treatment.

A total of 126 bleeds were noted during the study. The estimated annualized bleeding rate was 5.33 bleeds/patient/year (95% CI, 3.90-7.28). The success rate for treatment of bleeds (percentage of bleeds for which haemostatic response was rated as excellent or good) was 92.1% (116 of 126 bleeds).

Of the 63 patients, 32 patients (50.8%) experienced at least 1 adverse event during the study. Table 4-12 lists adverse events reported in $\geq 2.0\%$ of the patients.

Table 4-12. Adverse events reported in $\geq 2.0\%$ of the patients (safety analysis set : N=63)

	n (%)			n (%)	
Ear pain	2	(3.2)	Varicella	2	(3.2)
Toothache	3	(4.8)	Contusion	4	(6.3)
Vomiting	4	(6.3)	Excoriation	2	(3.2)
Pyrexia	3	(4.8)	Underdose	2	(3.2)
Gastroenteritis viral	3	(4.8)	Headache	4	(6.3)
Nasopharyngitis	5	(7.9)	Cough	2	(3.2)
Upper respiratory tract infection	5	(7.9)	Rhinitis allergic	3	(4.8)

N: number of participants

n: number of patients with adverse events

Two adverse events probably or possibly related to the study drug were reported in 1 patient. The adverse events were contusion and incorrect dose administered (1 event each). Both were not serious adverse events, and were mild or moderate in severity.

During the study period, 3 serious adverse events (soft tissue injury, gastroenteritis viral, and device related infection [1 event each]) were reported in 3 patients (4.8%), and were considered by the investigator as unlikely related to the study drug. No deaths were reported during the study period.

4.(iii).A.(2).3 Extension study (5.3.5.2.3: Study NN7008-3568, from October 2009 and ongoing. Cutoff date: November 21, 2011)

A multicenter, open-label non-controlled study was conducted in 53 institutions in 18 countries including Japan in order to evaluate the long-term safety and efficacy in prevention and treatment of bleeds of turoctocog alfa in patients who completed Trial 3543, 3545, 3600, or 3893.

For prevention of bleeds, patients received turoctocog alfa at 20 to 50 IU/kg every second day or 20 to 60 IU/kg 3 times weekly according to the plasma FVIII trough level at the investigator's discretion. The dose for treatment of bleeds was adjusted to achieve a post-injection level of at least 0.50 IU/mL of plasma FVIII activity. For the treatment of a severe bleed, higher doses up to a total dose of 150 IU/kg per day could be used at the investigator's discretion (the dose was changed to "200 IU/kg per day" during the study). Patients who had to undergo surgical procedures during the study period were enrolled in the sub-trial to investigate the safety and efficacy of turoctocog alfa in prevention and treatment of bleeding during surgical procedures in patients with haemophilia A. On the day of surgery and until Day 7, turoctocog alfa was dose adjusted aiming for a trough plasma FVIII level or steady-state FVIII concentration of >0.50 IU/mL. From Day 8 to the day of returning to preventive treatment (including both prevention and treatment of bleeds), the dose was adjusted at the investigator's discretion.

A total of 189 patients were enrolled in the study by the cut-off date of November 21, 2011, and 187 patients received turoctocog alfa and were included in the safety analysis set and the full analysis set. The number of turoctocog alfa exposure days per patient was 88.3 ± 86.9 days (mean \pm SD), ranging from 1 to 363 days.

No patients developed FVIII inhibitors ≥ 0.6 BU/mL, the primary endpoint of the study, during the study period.

The efficacy of turoctocog alfa in preventing and treating bleeds, secondary endpoints of the study, were evaluated on the basis of the estimated annualized bleeding rate for prevention and a predefined 4-point scale (Table 4-9) for treatment.

In the sub-trial, haemostatic response to turoctocog alfa during and after surgery was evaluated using a predefined 4-point scale (Table 4-10).

A total of 366 bleeds were treated by the cut-off date. The estimated annualized bleeding rate of the total bleeding episodes was 3.54 bleeds/patient/year (95% CI, 2.90-4.33). The success rate for treatment of bleeds (percentage of bleeds for which haemostatic response was rated as excellent or good) was 87.2% (319 of 366 bleeds). Two major surgeries were performed. The surgery indications were pain in the left ankle, and poly-trauma. Haemostasis was successful (haemostatic effect was rated as excellent or good) in both patients during and after surgery.

Until the cut-off date, 40.6% (76 of 187) of the patients experienced at least 1 adverse event during the study. Table 4-13 lists adverse events reported in $\geq 2.0\%$ of the patients. During the surgery period, both vomiting and arthralgia were reported in 1 patient each.

Table 4-13. Adverse events reported in $\geq 2.0\%$ of the patients (safety analysis set, n=187)

	n (%)	
Nasopharyngitis	7	(3.7)
Contusion	4	(2.1)
Arthralgia	9	(4.8)
Oropharyngeal pain	6	(3.2)
Cough	5	(2.7)
Headache	6	(3.2)
Pyrexia	4	(2.1)

N: number of participants

n: number of patients with any adverse event

Three adverse events probably or possibly related to the study drug were reported in 2 patients. These adverse events were alanine aminotransferase increased, aspartate aminotransferase increased, and oedema peripheral (1 event each), and were mild or moderate in severity. During the surgical period, no adverse events probably or possibly related to the study drug were reported.

During the study period, 11 serious adverse events were reported in 8 patients (4.3%). The serious adverse events were injury, psychotic disorder, scrotal pain, fall (complicated with femur fracture and hand fracture), muscle haemorrhage, intestinal haemorrhage, skin injury, road traffic accident, and cellulitis (1 event each), and were considered by the investigator as unlikely related to the study drug. No deaths were reported during the study period.

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

4.(iii).B.(1) Data for review

4.(iii).B.(1).1 Safety and efficacy evaluation

As FVIII deficiency is a bleeding disorder caused by a quantitative decrease in or a qualitative abnormality of intrinsic FVIII, FVIII products are used to achieve the level of FVIII for adequate haemostasis in patients with FVIII deficiency. Accordingly, PMDA considers as follows: For clinical evaluation of turoctocog alfa as a new FVIII product, the efficacy can be assessed by studies comparing turoctocog alfa with conventional FVIII products with proven efficacy in terms of the pharmacokinetics and pharmacological activities. In addition, the haemostatic effect etc. of turoctocog alfa is to be assessed based on the results of clinical studies in patients with FVIII deficiency, and the safety is to be evaluated in terms of whether or not the differences in the amino acid sequence or glycosylation structure of turoctocog alfa may lead to the development of FVIII inhibitors (anti-FVIII neutralizing antibodies). Turoctocog alfa is activated by thrombin to form activated FVIII in the same manner as the intrinsic FVIII, and there are no differences between Japanese and non-Japanese patients with haemophilia including haemophilia A in terms of intrinsic and extrinsic ethnic factors such as epidemiological backgrounds, pathological conditions of bleeding tendency, and therapy

concepts for prevention of bleeding. Based on these facts, there are no concerns with the acceptance of the results of foreign clinical studies.

4.(iii).B.(1).2 Efficacy evaluation of global phase III studies

Among the clinical studies submitted, two studies enrolled Japanese patients: a global phase III study in previously treated patients ≥ 12 years with severe haemophilia A (Trial 3543), and an extension trial for patients completing Trial 3543 (Trial 3568). The predefined primary objective and primary endpoint of Trial 3543 were to assess the efficacy of turoctocog alfa for treatment and prevention of bleeds. However, during the study period, the primary objective and endpoint were changed to the incidence rate of FVIII inhibitors, and the efficacy evaluation was included as a secondary endpoint. PMDA requested the applicant to explain the reason why the primary endpoint was changed in Trial 3543.

The applicant responded as follows:

The predefined primary endpoint of Trial 3543 was to assess the efficacy of turoctocog alfa in treatment and prevention of bleeds in a descriptive manner. However, after Trial 3543 was started as a global clinical study, the US FDA requested the applicant to perform statistical evaluation of the development of FVIII inhibitors. Accordingly, the applicant changed the primary endpoint to the incidence rate of FVIII inhibitors (≥ 0.6 BU/mL), and conducted the study to demonstrate that the upper one-sided 97.5% confidence limit for the incidence rate of FVIII inhibitor to be below 6.8%. Efficacy evaluation in a descriptive manner was included as a secondary endpoint.

PMDA considers as follows:

It is undesirable to change the primary objective and endpoint of a clinical study after it has begun, because primary objective and endpoint affect study design significantly. However, considering the limited number of patients with haemophilia A who may be enrolled in clinical studies of turoctocog alfa, it is understandable to design the trial as a study to assess the efficacy of turoctocog alfa in a descriptive manner. It is feasible to review the efficacy of turoctocog alfa to a certain extent according to the results of efficacy assessment conducted as a secondary endpoint in Trial 3543. The incidence rate of FVIII inhibitors, which was set as the primary endpoint in Trial 3543, is a valuable measure in the efficacy and safety assessment of FVIII products.

4.(iii).B.(2) Efficacy

4.(iii).B.(2).1 Evaluation of turoctocog alfa as a FVIII product

In the clinical pharmacology studies, the pharmacokinetic parameters of turoctocog alfa based on FVIII activity were compared with those of Advate, a FVIII product available in Japan (See "4.(ii) Summary of clinical pharmacology studies"). PMDA has concluded that turoctocog alfa is expected to be effective as a FVIII product since no apparent differences in pharmacological activity and pharmacokinetics were noted between turoctocog alfa and Advate in the clinical pharmacology studies.

4.(iii).B.(2).2 Efficacy of turoctocog alfa in treatment of bleeds

In the clinical studies of turoctocog alfa, the efficacy of turoctocog alfa in treating bleeds was evaluated using a 4-point scale (Table 4-9), and the success rate for treatment of bleeds (the percentage of bleeds for which haemostatic response was rated as excellent or good) was assessed. The success rate for treatment of bleeds was as high as 80.8% (403 of 499 bleeds) in Trial 3543, 92.1% (116 of 126 bleeds) in Trial 3545, and 87.2% (319 of 366 bleeds) in Trial 3568. PMDA requested the applicant to explain the efficacy of turoctocog alfa as compared with conventional FVIII products.

The applicant responded as follows:

In Trial 3543, the success rate for treatment of bleeds was 84.5% (403 of 477), excluding bleeds with no outcome reported. The results were comparable to those of other FVIII products including Advate (81.2-95.1%). The percentage of bleeds that were stopped with 1 or 2 infusions, a more objective measure of efficacy, ranged from 86.7 to 94.9% for other FVIII products including Advate (*Haemophilia*. 2004;10:428-37, *J Thromb Haemost*. 2008;6:1319-26, *Thromb Haemost*. 2000;83:811-6, *Haemophilia*. 2009;15:869-80) and was 89.4% (446 of 499) for turoctocog alfa in Trial 3543.

PMDA has concluded that turoctocog alfa is expected to be effective in patients with haemophilia A including children since this drug shows high success rates in the treatment of bleeds in Trials 3543 and 3545. Although the comparison with other FVIII products is based on published literature data, PMDA considers that the efficacy of turoctocog alfa is comparable to conventional FVIII products including Advate.

4.(iii).B.(2).3 Efficacy of turoctocog alfa when used in surgery

Turoctocog alfa was administered during surgery in Part C of Trial 3543 and a sub-trial of Trial 3568. As efficacy evaluation, haemostatic response during surgery was evaluated using a 4-point scale (Table 4-10). In these trials, the dose of turoctocog alfa was selected at the investigator's discretion, and there were no clear criteria for dose selection. However, FVIII replacement therapy is indispensable in patients with haemophilia A undergoing surgery, and haemostatic response was rated as excellent or good in all patients who received turoctocog alfa during surgery, specifically, in 9 patients (8 and 1 patients undergoing major and minor surgeries, respectively) in Trial 3543, and 2 patients undergoing major surgery in Trial 3568. PMDA has concluded that turoctocog alfa is expected to be effective when used during surgery.

4.(iii).B.(2).4 Efficacy of turoctocog alfa for bleeding prevention

In Trial 3543, turoctocog alfa was administered regularly to prevent bleeds, and was assessed on the basis of the estimated annualized bleeding rate. PMDA requested the applicant to explain the significance of the study results.

The applicant responded as follows:

The efficacy of turoctocog alfa for bleeding prevention was demonstrated by comparing its estimated annualized bleeding rate with those calculated with historical data. The historical data used were selected from 37 reports reviewed in a meta-analysis on treatments for haemophilia by the Swedish Council on Health Technology Assessment (Hemophilia A and B and von Willebrand Disease - a systemic review (SBU), *Haemophilia*. 2012;18:158-65) based on the following criteria: (1) the subjects included in the study were patients with haemophilia A with an intrinsic FVIII activity of <2%, (2) the investigators defined and described FVIII replacement therapy, and (3) the mean annualized bleeding rate is reported or can be calculated using the results described in the report. As a result, nine reports were selected (*Semin Hematol*. 2001;38 Suppl 4:52-9, *Haemophilia*. 2003;9:38-49, *Thromb Haemost*. 2000;83:811-6, *N Engl J Med*. 2007;357:535-44, *N Engl J Med*. 1990;323:1800-5, *Haemophilia*. 2004;10:428-37, *Haemophilia*. 2007;13:9-11, *Haemophilia*. 2009;15:869-80, and *Haemophilia*. 2005;11:444-51). The characteristics of patients as historical controls, such as the severity of haemophilia, age, race/ethnicity, and the use of FVIII replacement therapy, were similar to those of patients enrolled in Trials 3543, 3545, and 3568. The estimated annualized bleeding rate, when pooling data from Trials 3543, 3545, and 3568, was 4.89 bleeds/patient/year, and was comparable to the rate obtained using the historical data (6.4 bleeds/patient/year). Among the 9 reports, 5 reports contained data that can be used to estimate an annualized bleeding rate in patients receiving FVIII products for treatment of bleeds only. The estimated annualized bleeding rate in this patient population was 22.0 bleeds/patient/year. On the other hand, the corresponding rate (mean \pm SD) calculated retrospectively in patients who had received FVIII products only for treatment of bleeds before enrolment in Trials 3543 and 3545 was 51.5 ± 42.2 and 30.4 ± 21.7 bleeds/patient/year, respectively.

PMDA considers as follows:

Although the appropriateness of using pooled data only to analyze the efficacy of turoctocog alfa is questionable, it has been concluded that the estimated annualized bleeding rate (6.50, 5.33, and 3.54 bleeds/patient/year in Trials 3543, 3545, and 3568, respectively) is comparable to the rate calculated from the literature on conventional FVIII products (6.4 bleeds/patient/year). The estimated annualized bleeding rates in these studies were substantially lower than those obtained from patients who received turoctocog alfa only for treatment of bleeds, suggesting that routine prophylactic treatment with turoctocog alfa decreased bleeding frequency in a degree similar to that with conventional FVIII products. Accordingly, PMDA has concluded that routine prophylactic treatment with turoctocog alfa is expected to be effective in preventing bleeds. The applicant should have consulted with PMDA at an appropriate time regarding the amendment to study protocol including study design, and discussed with PMDA about the method of efficacy evaluation in treatment of bleeds.

4.(iii).B.(3) Consistency of results between Japanese patients and the total study population

PMDA considers that there are no racial/ethnic factors that may affect the safety and efficacy evaluation of turoctocog alfa as no reports have pointed out any racial/ethnic differences in

pathophysiology and disease status of haemophilia A, current treatment regimens, or efficacy of FVIII products.

PMDA requested the applicant to explain consistency of the efficacy results between the Japanese patients and the total study population in Trial 3543.

The applicant responded as follows:

Efficacy results are consistent between the Japanese patients and the total study population on the basis of the following discussion on the higher success rates for treatment and prevention of bleeds (Table 4-14) and the lower estimated annualized bleeding rate in Japanese patients than in the total study population.

Table 4-14. Results of efficacy evaluation in Trial 3543 (full-analysis set)

Efficacy measure	Japanese patients (N = 9)	All patients (N = 150)
Success rate for treatment of bleeds ¹	100% (6/6 bleeds)	84.5% (403/477 bleeds)
Percentage of bleeds stopped with 1 or 2 infusions	100% (6/6 bleeds)	89.4% (446/499 bleeds)
Estimated annualized bleeding rate Mean [95% CI]	1.34 bleeds/patient/year [0.54, 3.31]	6.50 bleeds/patient/year [5.30, 7.97]

N: number of participants

1: Success rate for treatment of bleeds, excluding bleeds for which there was no outcome reported

Patients who had received only prophylactic treatment with conventional FVIII products prior to participation in this study accounted for 78% (7 of 9) of the Japanese patients and 35% (52 of 150) of the total study population. A retrospective evaluation of conditions of the joint according to the medical history and physical findings at screening revealed that haemophilic arthropathy was present in 7 of the 9 Japanese patients (78%) and 126 of all 150 participants (84%). It is difficult to identify the exact reasons for the lower estimated annualized bleeding rate in the Japanese patients, but it may be partially attributable to the fact that many of the Japanese patients had received prophylactic treatment with FVIII products and thus maintained good conditions of the joint.

PMDA considers that the following explanation provided by the applicant is acceptable: The efficacy findings obtained in Trial 3543 in terms of the success rate in treatment of bleeds and the estimated annualized bleeding rate are consistent between the Japanese patients and the total study population, and the lower estimated annualized bleeding rate in the Japanese patients than in the total study population may be attributable to a difference in patient characteristics.

4.(iii).B.(4) Safety

4.(iii).B.(4).1 Development of FVIII inhibitors during treatment with turoctocog alfa

The applicant described the development of neutralizing antibodies (FVIII inhibitors) against turoctocog alfa during treatment as follows:

In Trial 3543, 142 patients underwent a treatment of ≥ 75 exposure days, and 148 patients a treatment of ≥ 50 exposure days. In this study where the primary endpoint was the incidence rate of FVIII inhibitors, no patients developed FVIII inhibitors. In Trial 3568 with the primary endpoint of the incidence rate of FVIII inhibitors, a total of 187 patients received turoctocog alfa, but no patients developed FVIII inhibitors as of the cut-off date of November 21, 2011. In Trial 3809, a currently ongoing phase III clinical study in patients with severe haemophilia A with no history of treatment with FVIII products, a development of FVIII inhibitors in 1 patient was reported as an adverse reaction to turoctocog alfa.

In Trial 3545 in children, 63 pediatric patients received turoctocog alfa. Of these, 59 pediatric patients received a treatment of ≥ 50 exposure days. In 1 patient, blood test at Visit 4 was positive for FVIII inhibitors (1.3 BU/mL), but was negative on a retest, meaning that the definition of development of FVIII inhibitors was not met. As this patient received another FVIII product, the study was discontinued after 20 exposure days. As of the cut-off date, the number of exposure days for the 3 patients treated for a shorter duration was 49, 48, and 43 days.

PMDA considers as follows:

Currently available data from clinical studies of turoctocog alfa suggest that there are no reported cases of the development of FVIII inhibitors that may affect whether the product is approved or not. However, any FVIII products may induce the development of FVIII inhibitors, and the information on the development of FVIII inhibitors is extremely important. Therefore, when any relevant information is obtained from the ongoing Trial 3809 in children with haemophilia A with no prior history of FVIII therapy and post-marketing surveillance, the applicant should make the information available in clinical practice promptly, whenever necessary.

4.(iii).B.(4).2 Adverse event related to administration

As patients with haemophilia A inject conventional FVIII products themselves at home, in Trials 3543, 3545, and 3568, turoctocog alfa was administered by patients themselves or caregivers at home after due training. As a result, 22 medication errors (incorrect doses and/or procedures) were reported in 18 patients (12.0%) in Trials 3543, 5 medication errors in 4 patients (6.3%) in Trials 3545, and 2 medication errors in 2 patients in Trials 3568. Among the 18 patients reported to have medication errors in Trial 3543, 2 patients were aged 12 to 17 years and 16 patients were ≥ 18 years. The nature of errors was incorrect doses (overdoses and/or insufficient doses) in 20 events, and "wrong technique in drug usage process" (wrong dilution concentration in 1 event, and infusion site extravasation in 1 event). No events of medication errors were reported in Japanese patients.

PMDA assessed the safety of overdose with turoctocog alfa, and has confirmed that no clinically significant adverse events have occurred, although the number of relevant patients is limited. In Trials 3543 and 3545, medication errors occurred in several patients in certain institutions, and there were specific patients who experienced medication errors twice or more. However, in Trial 3568 where

patients who completed these trials were enrolled, the incidence of medication errors tended to decrease. PMDA considers that health care professionals should properly instruct patients how to use turoctocog alfa, which is assumed to be administered through self-injections at home, to prescribe the drug after confirming the appropriateness of the patient's self-injection procedures.

4.(iii).B.(4).3 Safety in children

The applicant described the safety of turoctocog alfa in children with haemophilia A as follows:

Adverse events following the use of turoctocog alfa in prevention and treatment of bleeds in Trials 3522, 3893, 3600, 3543, 3545, and 3568 by the cut-off date were analyzed by age group. The numbers of adverse events and patients with adverse events were 54 events in 19 of 31 patients (61.3%) aged <6 years, 46 events in 18 of 32 patients (56.3%) aged 6 to 11 years, 66 events in 19 of 24 patients (79.2%) aged 12 to <18 years, and 337 events in 98 of 127 patients (77.2%) aged ≥18 years. The number of reported adverse events per patient per year was 3.53 events/patient/year for patients aged <6 years, 2.44 events/patient/year for patients aged 6 to 11 years, 2.71 events/patient/year for patients aged 12 to <18 years, and 2.30 events/patient/year for patients aged ≥18 years. The number was highest in children <6 years among the age groups evaluated. Adverse events reported more frequently in children <6 years than children ≥6 years were as follows: upper respiratory tract infection (16.1%, 5 of 31 children <6 years vs. 3.3%, 6 of 183 children ≥6 years), pyrexia (9.7%, 3 of 31 children <6 years vs. 5.5%, 10 of 183 children ≥6 years), vomiting (9.7%, 3 of 31 children <6 years vs. 1.1%, 2 of 183 children ≥6 years), and cough (9.7%, 3 of 31 children <6 years vs. 3.8%, 7 of 183 children ≥6 years). As of the cut-off date, FVIII inhibitors did not develop in any age group, and the safety profile did not differ between children and adults.

PMDA has concluded that turoctocog alfa is tolerable in children as well. There are only limited data on the higher incidence of adverse events in children <6 years of age in the clinical studies, and the cause of this finding cannot be clarified. PMDA considers that information should continuously be collected during post-marketing use of the drug product. PMDA considers that there is no difference in safety profile between children and adults.

4.(iii).B.(5) Indications

PMDA has concluded that turoctocog alfa is expected to be effective in prevention and treatment of bleeds and during surgery in patients with severe haemophilia A as the results are comparable to those of conventional FVIII products approved in Japan, and that the clinical positioning of turoctocog alfa should be similar to conventional FVIII products.

The indication proposed at the time of submission of the application was "haemophilia A (congenital blood coagulation factor VIII deficiency)." Turoctocog alfa is intended to be used in not only patients with haemophilia A but also in those with acquired haemophilia A, who were not enrolled in clinical studies, with a low inhibitor potency and detectable plasma FVIII activity (*Japanese Journal of thrombosis and hemostasis*. 2011;22:295-322). As FVIII treatment policies for acquired haemophilia

As are similar to those for congenital haemophilia A, PMDA considers that turoctocog alfa should be effective for this patient population as well. Taking account of the indications of approved FVIII products, PMDA considers that "patients with blood coagulation factor VIII deficiency" is an appropriate description for the indication. PMDA considers that the description "control of bleeding tendency" is acceptable.

4.(iii).B.(6) Dose and administration

4.(iii).B.(6.1) Dosing regimens for treatment of bleeds and surgery

The applicant explained the proposed dosage regimens for treatment of bleeds and surgery as follows: The formula to calculate the required dose of factor VIII products for treatment of bleeds [Required units (IU) = body weight (kg) × desired factor VIII rise (% or IU/dL) × 0.5 (IU/kg per IU/dL)] as well as guidance for dosing in treatment of bleeding episodes and surgery were set based on the "Guideline on Core SPC for Human Plasma Derived and Recombinant Coagulation Factor VIII Products" developed by the European Medicines Agency (Rev.1, 2007 of EMEA/CPMP/BPWG/1619/1999, 1999) (hereinafter referred to as the "Core SPC Guideline"). This dose calculation formula is also indicated both in the "Guidelines for the Management of Haemophilia" published by the World Federation of Haemophilia (*Haemophilia*. 2013;19:e1-47) (hereinafter referred to as the "WFH guidelines"), and in the "Japanese Guideline for the Practical Replacement Therapy for Acute Bleeding and Surgical Prophylaxis in Haemophilia without Inhibitors" developed by the Haemophilia Unit of the Scientific Standardization Committee of the Japanese Society on Thrombosis and Haemostasis (hereinafter referred to as the "JSTH guidelines"). The pharmacokinetic profile after a single dose of turoctocog alfa was similar to that of Advate in Trial 3522. In Trial 3545, the pharmacokinetic profile after a single dose of turoctocog alfa in children was similar to that of FVIII products that were used before the study. On the basis of these facts, the applicant considered that the calculation formula and guidance for dosing in treatment of bleeds and surgery could be included in the Dosage and Administration section of labeling.

PMDA considers as follows:

It is understandable that the dose calculation formula described in the Core SPC Guidelines may be helpful to determine the dose of FVIII products for individual patients in treatment of bleeds or during surgery. However, the inclusion of a dose calculation formula in the Dosage and Administration section may pose a problem in terms of understandability. The dose calculation formula and guidance for dosing included in the applicant's proposed dosage and administration may be translated into 10 to 20 IU/kg, 15 to 30 IU/kg, and 30 to 50 IU/kg for the treatment of mild, moderate, and severe bleeding episodes, respectively, and 15 to 30 IU/kg and 40 to 50 IU/kg during minor and major surgery, respectively. The usual dose of turoctocog alfa should be 10 to 30 IU/kg, similar to those of the conventional recombinant FVIII products, Kogenate and Advate. Considering the fact that the dose of turoctocog alfa actually used (mean ± SD [range]) to treat bleeding episodes in the clinical study was 30.4 ± 10.8 (9.8-61.1) IU/kg per episode in Trial 3543, and 40.4 ± 16.6 (25.5-193.8) IU/kg per episode in Trial 3545, it is appropriate to state that the dose should be adjusted according to the severity of

FVIII deficiency, severity and location of bleeding, and clinical condition of the patient. The applicant may provide information on doses and dosing intervals by severity of bleeding episode, which were included in the proposed dosage and administration, in the package insert or other education materials.

4.(iii).B.(6).2) Dosing regimens for prevention of bleeds

The applicant explained the proposed dosage regimens for prevention of bleeds (routine prophylaxis) as follows:

In the protocols of the 3 clinical studies where patients received preventive treatment with turoctocog alfa, the dosage regimen was selected based on the WFH guidelines and the Core SPC Guideline and considering that the half-life of the drug may be shorter in younger patients. As the results of these 3 studies demonstrated the efficacy of preventive treatment with turoctocog alfa, the dosage regimen was selected as with those specified in the study protocols.

PMDA considers as follows:

Prophylactic treatment with FVIII products is recommended in international guidelines such as the WFH guidelines, those developed by the Medical and Scientific Advisory Council (MASAC) of the National Hemophilia Foundation (NHF) (MASAC Document #179, <http://www.hemophilia.org/sites/default/files/document/files/masac179.pdf>), and those by the United Kingdom Haemophilia Centre Doctors' Organization (UKHCDO) (*Br J Haematol.* 2010;149:498-507). Regarding the use of FVIII products approved in Japan, an MHLW-funded national survey has revealed that among patients with coagulation disorders, 1161 patients receive prophylactic treatment with conventional FVIII products more than once a week while 1167 patients do not, and details were unknown in 79 patients (the National Surveillance of Coagulation Disorders, Annual Report for FY 2012), indicating that several patients in Japan undergo routine prophylaxis. In Trial 3543, 148 patients including Japanese continued preventive treatment with ≥ 50 exposure days without any safety concerns [See "4.(i).B.(4) Safety"]. The dose range used in the clinical studies may be selected as the regimen for prophylaxis. Accordingly, PMDA has concluded that the applicant's proposed dosage regimen for prophylaxis is appropriate. Specifically, the regimen is as follows: For routine prophylaxis against bleeding in patients with severe haemophilia A, the usual recommended doses are 20 to 40 IU of factor VIII per kg body weight every second day or 20 to 50 IU of factor VIII per kg body weight 3 times weekly. For pediatric patients <12 years of age, doses of 25 to 50 IU of factor VIII per kg body weight every second day or 25 to 60 IU of turoctocog alfa per kg body weight 3 times weekly are recommended.

4.(iii).B.(6).3) Infusion rate

The applicant explained the proposed infusion rate to be included in the Dosage and Administration section as follows.

The WFH guidelines recommend that "FVIII should be infused by slow IV injection at a rate not to exceed 3 mL per minute in adults and 100 units per minute in young children." In clinical studies of

turoctocog alfa, an infusion rate of 1 to 2 mL/min was specified in the study protocols, and there were no infusion-related adverse events including acute reactions. On the basis of these findings, the following descriptions are proposed: Turoctocog alfa should be reconstituted with the entire volume of the supplied solvent, and the reconstituted solution should be administered as a slow intravenous injection at a rate of 1 to 2 mL/min.

PMDA accepted the applicant's explanation.

On the basis of the review in described in the sections 4.(iii).B.(6).1) to 4.(iii).B.(6).3), PMDA has concluded that the Dosage and Administration for labeling of turoctocog alfa should be as follows:

[Dosage and Administration]

The drug product should be reconstituted with the entire volume of the supplied solvent, and the reconstituted solution should be administered as a slow intravenous injection at a rate of 1 to 2 mL/min.

The usual dosage is 10 to 30 IU of turoctocog alfa per kg body weight for on-demand treatment of bleeding. The dosage may be adjusted according to the patient's condition.

For routine prophylaxis against bleeding in patients with severe haemophilia A, the usual dosage is 20 to 40 IU of turoctocog alfa per kg body weight every other day or 20 to 50 IU of turoctocog alfa per kg body weight 3 times weekly. The dosage for pediatric patients <12 years of age is 25 to 50 IU of turoctocog alfa per kg body weight every other day or 25 to 60 IU of turoctocog alfa per kg body weight 3 times weekly.

4.(iii).B.(7) Post-marketing surveillance

The applicant explained the contents of post-marketing investigations as follows:

As turoctocog alfa will be administered repeatedly for a long period of time, post-marketing information on the safety of long-term treatment should be collected. The development of FVIII inhibitors (neutralizing antibodies) is a major problem in FVIII replacement therapy, and it is important to specify risk factors for and outcome of the development of FVIII. The applicant will select these matters as priority investigation items. Since allergic reactions and hypersensitivity have been reported in clinical studies of turoctocog alfa as well as for conventional FVIII products, the applicant will collect information on these adverse events as a priority investigation item via the post-marketing surveillance.

Considering the number of patients with haemophilia A in Japan and the market share of currently available FVIII products, the number of patients who will receive turoctocog alfa may be limited. The applicant initially planned to conduct an all-case survey of turoctocog alfa after launch so that it could collect as much information as possible in order to investigate the risks listed as priority investigation

items, but changed the plan to ensure feasibility. The post-marketing survey will be conducted as a specified use-result survey with a target sample size of 30 patients, registration period of 4 years, and survey period of 6 years. Each patient will be observed for 2 years. The reason for conducting a specified use-result survey on long-term treatment is that, although the number of patients enrolled is small, efficacy and safety data on more than 1 bleeding episode may be obtained through the follow-up of each patient for 2 years, thereby allowing the priority investigation items to be evaluated.

PMDA considers as follows:

The applicant specified the development of FVIII inhibitors, which was the primary endpoint in the clinical studies, and hypersensitivity (e.g., allergy), which may inevitably occur as reaction to a protein, as priority investigation items in the post-marketing surveillance. However, the applicant has not clearly described how to analyze survey data, nor validated the length of survey period. Since turoctocog alfa is intended to be used for a longer period of time than the treatment period in clinical studies, in the post-marketing surveillance the applicant should compare safety profile of long-term exposure to turoctocog alfa with that of short-term exposure to assess the long-term safety of the drug. As the incidence of adverse events reported in clinical studies was high in children <6 years of age, PMDA considers that the applicant should enroll an appropriate number of children in the post-marketing surveillance, regardless of with or without treatment history.

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

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

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

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

GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.3.5.2, 5.3.5.2.1, 5.3.5.2.3). As a result, several findings were noted at some trial sites, such as the absence of a list of duties of the newly assigned investigator who replaced the previous investigator; inappropriate descriptions of written information for informed consent; the absence of records on the fact that information possibly influencing the patients' decision was provided to confirm their willingness to continue the study; and study protocol violations (violation of the provisions on the study drug administration). The inspection also revealed that the sponsor did not obtain consent from the newly assigned investigator on the contents of study protocol, and that the sponsor could not detect the inappropriate descriptions of written information of patients through monitoring. Although the above-mentioned findings were

identified as points for improvement, the data on the relevant subjects were handled appropriately. PMDA has concluded that the clinical studies have been conducted according to GCP, and there should be no problem with conducting a regulatory review based on the submitted application documents.

IV. Overall Evaluation

Based on the data submitted by the applicant, PMDA has concluded that the efficacy of turoctocog alfa in controlling bleeding tendency in patients with blood coagulation factor VIII deficiency can be expected, and that its safety is acceptable in view of its observed benefits. PMDA considers that turoctocog alfa is clinically meaningful as an option of treatment to control bleeding tendency in patients with blood coagulation factor VIII deficiency.

PMDA considers that the product may be approved when further review of efficacy, safety and post-marketing surveillance is made in the Expert Discussion and it is concluded that there are no particular problems.

Review Report (2)

October 31, 2013

I. Product Submitted for Registration

[Brand name]	NovoEight for Intravenous Injection 250, 500, 1000, 1500, 2000, and 3000
[Non-proprietary name]	Turoctocog Alfa (Genetical Recombination)
[Name of applicant]	Novo Nordisk Pharma Ltd.
[Date of application]	December 27, 2012

II . Content of the Review

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

Clinical studies (Study NN7008-XXXX) are expressed as Trial XXXX hereinafter.

(1) Efficacy in treatment of bleeds

PMDA has concluded that Turoctocog Alfa (Genetical Recombination) (hereinafter referred to as turoctocog alfa) is expected to be effective as a blood coagulation factor VIII (FVIII) product, since there were no apparent differences between turoctocog alfa and Advate in pharmacokinetics and pharmacological activity evaluated in Trial 3522. In clinical studies, the efficacy of turoctocog alfa in treatment of bleeds was evaluated using a prespecified criteria to calculate the success rate for treatment of bleeds. As high success rates were obtained, specifically 80.8% (403 of 499 bleeds) in 3543 Trial, 92.1% (116 of 126 bleeds) in Trial 3545, and 87.2% (319 of 366 bleeds) in Trial 3568, PMDA has concluded that turoctocog alfa is expected to be effective in treatment of bleeding in patients including children.

On the basis of the results of Trials 3543 and 3568, PMDA has concluded that turoctocog alfa is also expected to be effective for patients undergoing surgery.

The above conclusions of PMDA were supported by the expert advisors.

(2) Efficacy for bleeding prevention

PMDA considers as follows:

The estimated annualized bleeding rates in patients receiving routine prophylactic treatment with turoctocog alfa for prevention of bleeds in clinical studies (6.50, 5.33, and 3.54 bleeds/patient/year in Trials 3543, 3545, and 3568, respectively) are apparently lower than those in participants in Trials 3543 and 3545 during the period when they received FVIII products only for treatment of bleeds before participating in these trials (51.5 and 30.4 bleeds/patient/year in Trials 3543 and 3545, respectively), and that calculated from published literature (*Semin Hematol.* 2001;38 Suppl 4:52-9, *Haemophilia.* 2003;9:38-49, *Thromb Haemost.* 2000;83:811-6, *N Engl J Med.* 2007;357:535-44, *N Engl J Med.* 1990;323:1800-5) as the rate in patients who received conventional FVIII products only for treatment of bleeds (22.0 bleeds/patient/year). Also, these figures are similar to 6.4 bleeds/patient/year, which was calculated from published literature data as the rate in patients receiving routine prophylactic treatment with conventional FVIII product (*Semin Hematol.* 2001;38 Suppl 4:52-9, *Haemophilia.* 2003;9:38-49, *Thromb Haemost.* 2000;83:811-6, *N Engl J Med.* 2007;357:535-44, *N Engl J Med.* 1990;323:1800-5, *Haemophilia.* 2004;10:428-37, *Haemophilia.* 2007;13:9-11, *Haemophilia.* 2009;15:869-80, and *Haemophilia.* 2005;11:444-51). Accordingly, PMDA has concluded that routine prophylactic treatment with turoctocog alfa is expected to be effective in preventing bleeds.

The above conclusions of PMDA were supported by the expert advisors.

(3) Safety

Based on the currently available data, PMDA has concluded that turoctocog alfa is tolerable in patients including children. However, any FVIII products may induce the development of FVIII inhibitors, and information on the development of FVIII inhibitors is important. PMDA considers that the applicant will have to promptly provide healthcare professionals with updates of the currently ongoing Trial 3809 in foreign children with haemophilia A without history of FVIII therapy as well as post-marketing surveillance whenever necessary. There are only limited data on the higher incidence of adverse events in children <6 years of age in clinical studies, and the cause of this difference is unclear. PMDA considers that the applicant should collect information on adverse events in this patient population after the launch of the product.

The above conclusions of PMDA were supported by the expert advisors.

(4) Indications

PMDA has concluded that turoctocog alfa is expected to be effective in prevention and treatment of bleeds and during surgery in patients with haemophilia A on the basis of the submitted clinical study data, and that its clinical positioning should be similar to conventional FVIII products.

Turoctocog alfa is intended to be used in patients with haemophilia A (congenital blood coagulation factor VIII deficiency) as well as in those with acquired haemophilia A (acquired FVIII deficiency), who were not enrolled in the clinical studies, with a low inhibitor potency and detectable plasma FVIII activity (*Japanese Journal of Thrombosis and Hemostasis*. 2011;22:295-322). As FVIII treatment policies for acquired haemophilia A are similar to those for congenital haemophilia A, PMDA considers that turoctocog alfa should be effective for this patient population as well. Although the proposed indication is "control of bleeding tendency in patients with haemophilia A (congenital blood coagulation factor VIII deficiency)," PMDA has concluded that the target patient population should be specified as "patients with congenital blood coagulation factor VIII deficiency" by considering the fact that conventional FVIII products are indicated for "patients with congenital blood coagulation factor VIII deficiency to replace blood coagulation factor VIII in plasma and control bleeding tendency." PMDA considers that the description "control of bleeding tendency" is acceptable.

The above conclusions of PMDA were supported by the expert advisors.

PMDA instructed the applicant to change the description in the Indication section, and the applicant answered that it would change the indication to describe "control of bleeding tendency in patients with blood coagulation factor VIII deficiency."

(5) Dose and administration

1) Dosing regimens for treatment of bleeds and surgery

PMDA has concluded as follows:

On the basis of the submitted data, the clinical positioning of turoctocog alfa is similar to conventional FVIII products. Accordingly, it is appropriate to describe that "the usual dosage is 10 to 30 IU of turoctocog alfa per kg body weight. The dosage may be adjusted according to the severity of factor VIII deficiency, location and severity of bleeding as well as clinical condition of individual patients" in the Dosage and Administration section, and it is appropriate to consider the fact that the dose of turoctocog alfa actually used to treat bleeding episodes was 30.4 ± 10.8 (9.8-61.1) IU/kg in Trial 3543, and 40.4 ± 16.6 (25.5-193.8) IU/kg in Trial 3545. The applicant may provide information on doses and dosing intervals by severity of bleeding episode, which were included in the proposed dosage and administration, by specifying in the "Precautions for Dosage and Administration" section of the package insert and by using separated materials.

In the Expert Discussion, there was a comment that physicians adjust the dose of FVIII products for their patients with blood coagulation factor VIII deficiency according to the degree of bleeding, and providing detailed information in the Dosage and Administration section is rather undesirable. The conclusion by PMDA in terms of the dosage and administration was supported by the expert advisors.

2) Dosing regimens for prevention of bleeds

In Trial 3543, 148 patients including Japanese continued preventive treatment of ≥ 50 exposure days, and treatment was tolerable in terms of safety, and PMDA has concluded that routine prophylactic treatment with turoctocog alfa is expected to be effective in preventing bleeds. Accordingly, PMDA has concluded that the dose range used in the clinical studies may be selected as the regimen for routine prophylaxis.

The above conclusions of PMDA were supported by expert advisors.

The expert advisors provided the following opinions. PMDA has appropriately communicated these opinions to the applicant.

- Routine prophylactic treatment with currently available FVIII products to prevent bleeds has been recommended in international guidelines for the management of haemophilia, and this has been established as a common therapy in the clinical setting. It is desirable to specify the routine prophylactic treatment with turoctocog alfa in the Dosage and Administration section of labeling for turoctocog alfa, of which clinical positioning is similar to that of currently available FVIII products, in order to ensure the proper use of the product.
- It is becoming increasingly common that newly diagnosed patients with haemophilia receive prophylactic treatment with conventional FVIII products. Even when turoctocog alfa becomes the first FVIII product of which routine prophylaxis is included in the Dosage and Administration section, no confusion would occur in the clinical setting.
- PMDA should instruct the applicant not to promote turoctocog alfa, after market launch, as the first FVIII product that is allowed to include routine prophylaxis in the Dosage and Administration section.

PMDA requested to the applicant to explain the reason why routine prophylactic treatment with turoctocog alfa is indicated only for patients with severe haemophilia A. The applicant answered that routine prophylactic treatment with turoctocog alfa need not be limited to patients with severe haemophilia A.

3) Infusion rate

In clinical studies of turoctocog alfa, an infusion rate of 1 to 2 mL/min was specified in the study protocols, and was tolerable since there were no infusion-related adverse events including acute reactions. On the basis of these findings, PMDA considers it is appropriate to recommend to administer the drug at a rate of 1 to 2 mL/min according to the clinical study protocols.

The above conclusions of PMDA were supported by the expert advisors.

According to the above discussions outlined in the sections 1)-3), PMDA requested the applicant to change the descriptions of the Dosage and Administration section to the following:

[Dosage and Administration]

The product should be reconstituted with the entire volume of the supplied solvent, and the reconstituted solution should be administered as a slow intravenous injection at a rate of 1 to 2 mL/min.

The usual dosage is 10 to 30 IU of turoctocog alfa per kg body weight for on-demand treatment of bleeding. The dose may be adjusted according to the patient's clinical condition.

For routine prophylaxis, the usual dosage is 20 to 40 IU of turoctocog alfa per kg body weight every other day or 20 to 50 IU of turoctocog alfa per kg body weight 3 times weekly. The dosage for pediatric patients <12 years of age is 25 to 50 IU of turoctocog alfa per kg body weight every other day or 25 to 60 IU of turoctocog alfa per kg body weight 3 times weekly.

(6) Risk management plan (draft)

On the basis of the results of evaluation in the section "4.(iii).B.(7) Post-marketing investigations" of Review Report (1), PMDA considers that when the applicant conducts a specified use-result survey on long-term treatment of turoctocog alfa in order to assess the safety of long-term treatment with the drug, the applicant should clearly define how to evaluate the long-term safety of turoctocog alfa, and should prepare a study protocol which allows the applicant to collect and evaluate information that was not obtained during the clinical studies. Accordingly, PMDA has concluded that the following points should be investigated.

- In the evaluation of long-term safety of turoctocog alfa, adverse event profile and the incidence rate of FVIII inhibitors during long-term treatment with the drug should be compared with those during short-term treatment.
- Considering the fact that the incidence of adverse events was high among children <6 years of age and no Japanese children were enrolled in the clinical studies, the applicant should enroll an appropriate number of children in the survey.

The above conclusions of PMDA were supported by the expert advisors.

On the basis of the results of the Expert Discussion, PMDA requested the applicant to investigate the following points during the post-marketing surveillance of turoctocog alfa.

PMDA has concluded that the risk management plan for turoctocog alfa should include the safety and efficacy specifications listed in Table 1 and additional safety monitoring and risk minimization activities listed in Tables 2 and 3.

Table 1. Safety and efficacy specifications in risk management plan

Safety specifications		
Important identified risks	Important potential risks	Important missing information
<ul style="list-style-type: none"> Development of FVIII inhibitors Allergic/hypersensitivity reactions including shock and anaphylaxis 	Not applicable	<ul style="list-style-type: none"> Safety in patients with no history of FVIII therapy Safety of long-term treatment Safety in children
Efficacy specifications		
<ul style="list-style-type: none"> Efficacy of long-term treatment 		

Table 2. Outline of additional pharmacovigilance activities and risk minimization activities in risk management plan

Additional pharmacovigilance activities	Additional risk minimization activities
<ul style="list-style-type: none"> Early post-marketing phase vigilance Specified use-result survey on long-term treatment Post-marketing clinical studies¹ 	<ul style="list-style-type: none"> Early post-marketing phase vigilance

1 : After the approval of turoctocog alfa, ongoing Trial 3568 will be continued as a post-marketing clinical study until the drug will be commercially available in medical institutions.

Table 3. Outline of specified use-result survey on long-term treatment (draft)

Purpose	Confirm the safety and efficacy of long-term treatment with turoctocog alfa in the clinical setting
Survey method	Central registration
Participants	Patients with blood coagulation factor VIII deficiency
Observation period	2 years
Target sample size	30 patients (expected to include about 6 children)
Priority survey items	Development of FVIII inhibitors, incidence of allergic/hypersensitivity reactions including shock and anaphylaxis, and occurrence of adverse events and adverse reactions Efficacy of turoctocog alfa in treatment of bleeds, haemostatic effect of turoctocog alfa during and after surgery, and total dose of turoctocog alfa in treatment of bleeds, during surgery, and in routine prophylactic treatment.

(7) Quality

The 18-month data of long-term testing of the drug substance manufactured with Manufacturing Process D (drug substance formulation [REDACTED]) and the 18-month data of long-term testing of the drug product (conditions 4 and 5) were newly submitted [See "2.A. Summary of the submitted data" of Review Report (1)].

Based on the results of long-term testing of the drug substance manufactured with Manufacturing Process C (drug substance formulation [REDACTED]), a shelf-life of 24 months was proposed for the drug substance stored in low-density polyethylene bottle at [REDACTED]°C to [REDACTED]°C. Based on the results of long-term testing (conditions 1 and 2) of the drug product formulated using the drug substance manufactured with Manufacturing Process C (drug substance formulation [REDACTED]), a shelf-life of 24 months was proposed for the drug product stored at 2°C to 8°C. It was also proposed that the drug product may be stored at room temperature sometime during the 24-month shelf-life providing that products placed at room temperature will never be stored again at 2°C to 8°C and the storage period at room temperature should be up to 6 months.

[REDACTED]
[REDACTED] The applicant explained the appropriateness of setting the shelf-life of the drug substance as well

as the drug product formulated with the same drug substance, based on the long-term testing of the drug substance manufactured with Manufacturing Process C (drug substance formulation [REDACTED]) and its drug product as follows:

[REDACTED]

[REDACTED] Based on the results of a study on the effect of variation of concentration of excipients (\pm [REDACTED]%) on the stability of the drug product ([REDACTED] $^{\circ}$ C, [REDACTED] months), it was concluded that up to a [REDACTED]% variation of excipient concentration in the drug substance was acceptable.

Characterization of drug substances manufactured with Manufacturing Processes C and D revealed no differences between the 2 substances in terms of peak patterns of trypsin peptide mapping, carbohydrate structure and relative amount of N-glycan obtained with glycosylation mapping, mass peak pattern obtained with thrombin mapping, SDS-PAGE band pattern, RP-HPLC profile, and SE-HPLC profile. The results of specification tests of the drug substances manufactured with both processes have revealed that both drug products satisfy the drug product release specification, and that the amount of impurities in the drug substance manufactured with Manufacturing Process D is not larger than that with Manufacturing Process C.

The results of long-term testing ([REDACTED] months) of the drug substances manufactured with Manufacturing Processes C and D revealed that both drug products showed similar changes over time for [REDACTED] months. The applicant concluded that the difference between Manufacturing Processes C and D did not affect the stability of the drug substance. The applicant thus considers that it is appropriate to set shelf-lives of the drug substance and drug product of turoctocog alfa based on the long-term testing of the drug substance manufactured with Manufacturing Process C (drug substance formulation [REDACTED]) and the drug product formulated with the same drug substance.

[REDACTED]

[REDACTED] According to the review described in "2.B. Outline of the review by PMDA" of Review Report (1) as well as the above discussion, PMDA has concluded that the quality of the drug substance and drug product of turoctocog alfa are adequately controlled.

III. Overall Evaluation

Based on the above review, PMDA has concluded that turoctocog alfa may be approved after modifying the indication and the dosage and administration as shown below. The re-examination period is 8 years, neither the drug substance nor the drug product is classified as poisonous drugs or powerful drugs, and the product is classified as a biological product.

[Indications]	Control of bleeding tendency in patients with blood coagulation factor VIII deficiency
[Dosage and Administration]	<p>The product should be reconstituted with the entire volume of the supplied solvent, and the reconstituted solution should be administered as a slow intravenous injection at a rate of 1 to 2 mL/min.</p> <p>The usual dosage is 10 to 30 IU of turoctocog alfa per kg body weight for on-demand treatment of bleeding. The dosage may be adjusted according to the patient's clinical condition.</p> <p>For routine prophylaxis, the usual dosage is 20 to 40 IU of turoctocog alfa per kg body weight every other day or 20 to 50 IU of turoctocog alfa per kg body weight 3 times weekly. The dosage for pediatric patients <12 years of age is 25 to 50 IU of turoctocog alfa per kg body weight every other day or 25 to 60 IU of turoctocog alfa per kg body weight 3 times weekly.</p>