Report on the Deliberation Results

September 4, 2018
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Jivi for IV Injection 250, Jivi for IV Injection 500, Jivi for IV Injection 1000, Jivi for IV Injection 2000, Jivi for IV Injection 3000
Non-proprietary Name	Damoctocog Alfa Pegol (Genetical Recombination) (JAN*)
Applicant	Bayer Yakuhin, Ltd.
Date of Application	October 17, 2017

Results of Deliberation

In its meeting held on August 29, 2018, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is classified as a biological product, and the re-examination period is 8 years. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Condition of Approval

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

**Japanese Accepted Name (modified INN)*

Review Report

August 2, 2018
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Jivi for IV Injection 250, Jivi for IV Injection 500, Jivi for IV Injection 1000, Jivi for IV Injection 2000, Jivi for IV Injection 3000
Non-proprietary Name	Damoctocog Alfa Pegol (Genetical Recombination)
Applicant	Bayer Yakuhin, Ltd.
Date of Application	October 17, 2017
Dosage Form/Strength	Lyophilized powder for reconstitution for injection: Each vial contains 250, 500, 1000, 2000, or 3000 IU Damoctocog Alfa Pegol (Genetical Recombination).
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Definition	Damoctocog Alfa Pegol is a recombinant human blood coagulation factor VIII analogue (molecular weight, ca. 234,000) whose protein moiety corresponds to amino acids 1-754 and 1649-2332 of human blood coagulation factor VIII. Damoctocog Alfa Pegol is composed of an H chain consisting of 754 amino acid residues and an L chain consisting of 684 amino acid residues, and a polyethylene glycol polymer (average molecular weight, ca. 60,000) is attached to amino acid residue of the L chain at position 156 which was substituted by Cys via linker. The glycoprotein is composed of 1438 amino acid residues and produced in Baby hamster kidney cells.

Structure

Amino acid sequences and disulfide bonds:

H-chain

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ATRRYYLGAV ELSWDYMQSD LGELPVDARF PPRVPKSFPF 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 EAYVKVDSCP EEPQLRMKNN EEAEDYDDDL
TDSEMDVVRF DDDNSPSFIQ IRSVAKKHPK TWVHYIAAEE EDWDYAPLVL
APDDRSYKSQ YLNNGPQRIG RKYKKVRFMA YTDETFKTRE AIQHESGILG
PLLYGEVGDT LLIIFKNQAS RPYNIYPHGI TDVRPLYSRR LPKGVKHLKD
FPILPGEIFK YKWTVTVEDG PTKSDPRCLT RYYSSFVNME RDLASGLIGP
LLICYKESVD QRGNQIMSDK RNVILFSVFD ENRSWYLTEN IQRFLPNPAG
VQLEDPEFQA SNIMHSINGY VFDSLQLSVC LHEVAYWYIL SIGAQTDFLS
VFFSGYTFKH KMVYEDTLTL FPFSGETVFM SMENPGLWIL GCHNSDFRNR
GMTALLKVSS CDKNTGDYYE DSYEDISAYL LSKNNAIEPR SFSQNPPVLK
RHQR
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L-chain

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EITRTTLQSD QEEIDYDDTI SVEMKKEDFD IYDEDENQSP RSFQKKTRHY
FIAAVERLWD YGMSSSPHVL RNRAQSGSVP QFKKVVFQEF TDGSFTQPLY
RGELNEHLGL LGPYIRAEVE DNIMVTFRNQ ASRPYSFYSS LISYEEDQRQ
GAEPRCNFVK PNETKTYFWK VQHHMAPTKD EFDCKAWAYF SDVDLEKDVH
SGLIGPLLVC HTNTLNPAHG RQVTVQEFAL FFTIFDETKS WYFTENMERN
CRAPCNIQME DPTFKENYRF HAINGYIMDT LPGLVMAQDQ RIRWYLLSMG
SNENIHSIHF SGHVFTVRKK EEYKMALYNL YPGVFETVEM LPSKAGIWRV
ECLIGEHLHA GMSTLFLVYS NKCQTPLGMA SGHIRDFQIT ASGQYGQWAP
KLARLHYSGS INAWSTKEPF SWIKVDLLAP MIIHGIKTQG 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
```

Glycosylation: H-chain N41 and N239, L-chain N162 and N470

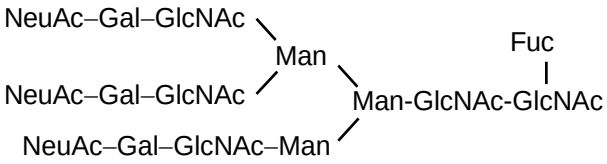
Sulfation: H-chain Y346, Y718, Y719, and Y723, L-chain Y16 and Y32

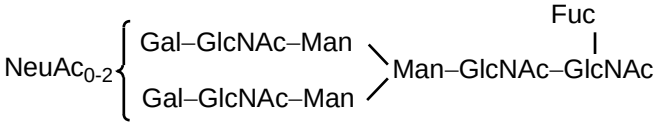
Partial sulfation: H-chain Y395

Main PEGylation site: L-chain C156

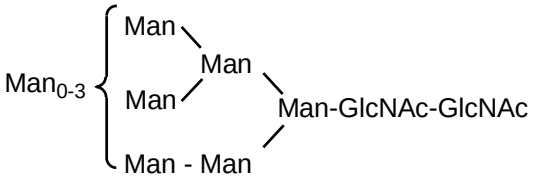
Main proposed carbohydrate structures

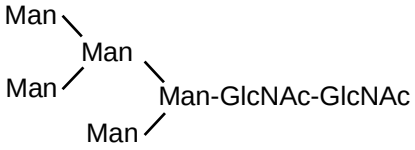
H-chain N41



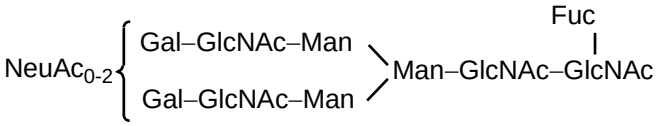


H-chain N239

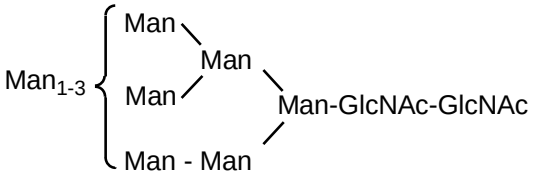




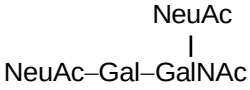
L-chain N162



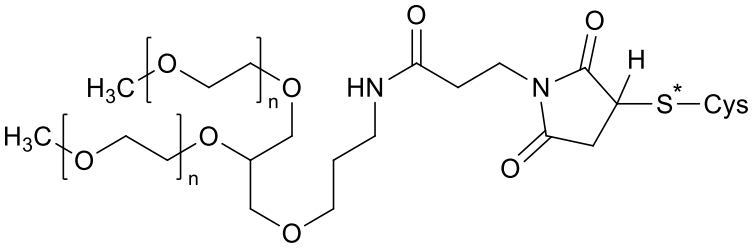
L-chain N470



O-linked glycan chain



Scheme of polyethylene glycol conjugation:



*Thiol group of Cys residue

Molecular formula: $C_{7445}H_{11318}N_{1984}O_{2184}S_{69}$ (protein moiety, 2 chains)
Molecular weight: ca. 234,000

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

Results of Review

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

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following condition. The safety and efficacy of the product in clinical practice need to be further investigated via post-marketing surveillance.

Indication

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

Dosage and Administration

The product should be reconstituted with the total volume of diluent supplied and infused by slow intravenous injection at a rate not exceeding 2.5 mL/min.

For patients aged ≥12 years, the usual dose is 10 to 30 IU/kg body weight. This may be adjusted according to the patient's condition.

For patients aged ≥12 years, the usual regimen for routine prophylaxis is 30 to 40 IU/kg body weight twice weekly. The regimen may be adjusted to 45 to 60 IU/kg body weight every 5 days or 60 IU/kg body weight once weekly, according to the patient's condition.

Condition of Approval

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

Attachment

Review Report (1)

June 12, 2018

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

Product Submitted for Approval

Brand Name	Jivi for IV Injection 250, Jivi for IV Injection 500, Jivi for IV Injection 1000, Jivi for IV Injection 2000, Jivi for IV Injection 3000
Non-proprietary Name	Damoctocog Alfa Pegol (Genetical Recombination)
Applicant	Bayer Yakuhin, Ltd.
Date of Application	October 17, 2017
Dosage Form/Strength	Lyophilized powder for reconstitution for injection: Each vial contains 250, 500, 1000, 2000, or 3000 IU Damoctocog Alfa Pegol (Genetical Recombination).

Proposed Indication

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

Proposed Dosage and Administration

The product should be reconstituted with the total volume of diluent supplied and infused by slow intravenous injection at a rate not exceeding 2.5 mL/min.

The usual dose is 10 to 30 IU/kg body weight. This may be adjusted according to the patient's condition.

The usual regimen for routine prophylaxis is 45 to 60 IU/kg body weight every 5 days. The dose and frequency may be adjusted to 60 IU/kg body weight once weekly or 30 to 40 IU/kg body weight twice weekly, according to the patient's condition.

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List of Abbreviations

See Appendix.

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

Hemophilia A (congenital factor VIII deficiency) is a bleeding disorder caused by deficiency or dysfunction of coagulation factor VIII (FVIII), and serious bleeding symptoms may occur. Standard treatment for hemophilia A patients is the infusion of exogenous FVIII concentrates needed for effective hemostasis. Currently in Japan, multiple human plasma-derived and recombinant FVIII concentrates have been approved as FVIII products.

Damoctocog Alfa Pegol (Genetical Recombination) (damoctocog alfa pegol) is a recombinant FVIII variant conjugated with an approximately 60-kilodalton (kDa) polyethylene glycol (PEG). Damoctocog alfa pegol was developed as a recombinant FVIII with an extended plasma elimination half-life and less frequent dosing achieved through PEGylation, compared to unmodified FVIII.

In the development of damoctocog alfa pegol, a global phase II/III study involving patients with hemophilia A between 12 and 65 years of age in 20 countries including Japan (Study 13024) was initiated in April 2012. Based on the results from this study etc., the applicant has now filed a marketing application for damoctocog alfa pegol. A biologics license application for damoctocog alfa pegol was submitted in August 2017 in the US and a marketing authorization application in September 2017 in the EU, and the both applications are under review as of June 2018.

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

2.1 Drug substance

2.1.1 Generation and control of cell substrate

The gene encoding B-domain deleted-recombinant human coagulation factor VIII (BDD-rFVIII), the protein moiety of damoctocog alfa pegol, was produced by obtaining a full-length FVIII gene from human [redacted] library and [redacted] encoding FVIII, followed by deletion of the FVIII B-domain gene and site-directed mutagenesis for site-specific conjugation of PEG. This gene was inserted into an expression vector, the obtained expression construct was transfected into Baby Hamster Kidney 21 (BHK-21) cells, and a suitable cell clone was isolated. This cell clone was used to prepare a master cell bank (MCB) and a working cell bank (WCB).

The MCB, WCB, and cells at the limit of *in vitro* cell age used for production (CAL) were characterized and subjected to purity tests in accordance with ICH Q5A (R1), Q5B, and Q5D. As a result, the genetic stability of the cell banking system and during production was demonstrated. No viral or non-viral adventitious agents were detected other than endogenous retrovirus-like particles, which are known to be present in rodent cell lines, in any of the tests conducted.

The appropriate storage conditions for the MCB and WCB have been established. There is no plan for generating a new MCB or WCB.

2.1.2 Manufacturing process

The manufacturing process for the drug substance consists of cell propagation, cell expansion (L bioreactor), production culture (L bioreactor), harvest, isolation by chromatography , virus inactivation by treatment, freezing/storage of the active substance intermediate, thawing/filtration and dilution of the active substance intermediate, immunoaffinity chromatography, chromatography, and filtration for virus removal by chromatography , and PEGylation, chromatography, final formulation, specification tests, filling, and freezing. The obtained drug substance is stored at °C using made of .

Virus inactivation by treatment, by chromatography , and filtration for virus removal have been defined as critical steps.

Process validation of the commercial-scale drug substance manufacturing process has been performed.

2.1.3 Safety evaluation of adventitious agents

In the manufacture of the drug substance, in addition to host BHK-21 cells, anti-human FVIII monoclonal antibodies produced by mouse hybridoma cells are used at the immunoaffinity chromatography step, both of which were demonstrated to conform to the Standard for Biological Ingredients.

Purity tests were performed on the MCB, WCB, and CAL, and no contamination with adventitious agents was detected [see Section 2.1.1].

Cell culture media from L and L bioreactors at commercial scale were tested for mycoplasma, sterility, adventitious viruses, and mouse minute virus (MMV), and no adventitious viruses or non-viral adventitious agents were detected. Tests for mycoplasma, sterility, adventitious viruses, and MMV are included as in-process controls for cell culture media from L and L bioreactors.

Viral clearance studies of the purification process were performed with model viruses. The results demonstrated a certain robustness of the purification process, as shown in Table 1.

For calculation of virus reduction factors of the process steps in Table 1, the lowest virus reduction factor value from multiple independent determinations for each of the process steps (including the results obtained with the regenerated resin for the immunoaffinity chromatography step and chromatography step) was adopted.

Table 1. Results of viral clearance studies of purification process

Process step	Virus reduction factor (log10)			
	Xenotropic murine leukemia virus (X-MuLV)	Pseudorabies virus (PRV)	Porcine parvovirus (PPV)	Reovirus type 3 (Reo 3)
[redacted] treatment	[redacted]	≥[redacted]	Not tested	Not tested
Immunoaffinity chromatography	[redacted][a]	[redacted][a]	[redacted]	[redacted]
[redacted] chromatography	[redacted]	[redacted]	[redacted]*	[redacted]*
Filtration for virus removal	≥[redacted]	≥[redacted]	≥[redacted]	≥[redacted]
Overall reduction factor	≥13.50	≥14.94	≥9.48	≥8.57

*: Not used for calculation of overall reduction factor.
a: Prepared by manufacturing process not including [redacted] and tested.

2.1.4 Manufacturing process development

The following are major changes made to the drug substance manufacturing process during development (Process A, Process B, Process C [the proposed commercial process]).

- Process A→Process B: changes at [redacted] step ([redacted] of [redacted]), [redacted] of [redacted] step, change in [redacted] of [redacted] step, [redacted] of [redacted] step (change from [redacted] step to [redacted] step)
- Process B→Process C: change at [redacted], [redacted] at [redacted] step ([redacted] of [redacted]) and [redacted] at [redacted] step

The drug product produced from the drug substance manufactured by Process [redacted] was used in non-clinical and phase I studies, and the drug product produced from the drug substance manufactured by Process [redacted] was used in phase II/III and phase III studies. For process changes, comparability of quality attributes between pre-change and post-change drug substances has been demonstrated.

Quality by design (QbD) approaches were used to develop the manufacturing process [see Section 2.3].

2.1.5 Characterization

2.1.5.1 Structure and properties

Characterization was performed as shown in Table 2, using [redacted] chromatography eluate before PEGylation, the drug substance, or the drug product.

Table 2. Overview of characterization

Attribute	
Structure	· Primary structure, disulfide bonds, free cysteine residues · PEGylation site · Amino acid modifications (tyrosine sulfation, methionine oxidation, asparagine deamidation, lysine glycation) · Glycosylation (N-linked glycans, O-linked glycans) · Domain structure, secondary structure, higher-order structure
Physicochemical properties	· Molecular weight · Far-ultraviolet circular dichroism spectrum · Differential scanning calorimetry (melting temperature) · Intrinsic fluorescence
Biological properties	· FVIII activity (chromogenic substrate assay, one-stage clotting assay) · Structural changes by thrombin · FX activation · Structural changes by FXa · Binding to von Willebrand Factor (vWF) · Formation of FIXa-FVIIIa complex (binding of activated FVIII to FIXa) · Structural changes of damoctocog alfa pegol (activated) by activated protein C (APC)

2.1.5.2 Product-related substances/Product-related impurities

Based on the results of characterization etc., [redacted] was considered a product-related substance. Aggregates, Impurity A, Impurity B, Impurity C ([redacted]), molecular species detected at around [redacted] kDa by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), [redacted] (Impurity D, Impurity E, Impurity F), and an oxidation variant (a methionine oxidation variant) were considered product-related impurities. The product-related impurities are adequately controlled by the drug substance and drug product specifications.

2.1.5.3 Process-related impurities

Host cell protein (HCP), host cell DNA, mouse immunoglobulin G (IgG), Impurity G, Impurity H, [redacted] (Impurity I, Impurity J, Impurity K, Impurity L, Impurity M, Impurity N, Impurity O, and Impurity P), Impurity Q, Impurity R, Impurity S, Impurity T, Impurity U, and Impurity V were considered process-related impurities. Except for HCP, Impurity G, Impurity I, and Impurity J, all of the process-related impurities have been demonstrated to be adequately removed by the manufacturing process. The safety of residual amounts of HCP, Impurity G, Impurity I, and Impurity J has been evaluated. HCP, host cell DNA, and mouse IgG are controlled by in-process testing. Impurity V is controlled by the drug substance specification, and bacterial endotoxins and microbes are controlled by the drug substance and drug product specifications.

2.1.6 Control of drug substance

The proposed specifications for the drug substance consist of content, description, identification ([redacted], peptide map), osmolarity, pH, purity ([redacted], [redacted], Impurity V), bacterial endotoxins, microbial limits, and assay (specific activity [chromogenic substrate assay]).

2.1.7 Stability of drug substance

The primary stability studies on the drug substance are shown in Table 3.

Table 3. Overview of primary stability studies on drug substance

	No. of batches	Storage conditions	Testing period	Storage package
Long-term	[redacted]	[redacted] ± [redacted] °C	[redacted] months [a]	[redacted] made of [redacted]
Accelerated	[redacted]	5± [redacted] °C	[redacted] weeks	
Stress (temperature)	[redacted]	25± [redacted] °C, [redacted] ± [redacted] %RH	[redacted] weeks	

a: ongoing through [redacted] months

The long-term testing showed no significant changes in quality attributes throughout the testing period, and the batches met the specifications.

In the accelerated testing, a decrease in [redacted] and changes in [redacted] (out of specification [redacted] for [redacted], an increase in [redacted]) were observed, and the drug substance was unstable. In the stress testing, a decrease in [redacted], a decrease in [redacted] ([redacted]), and changes in [redacted] (out of specification [redacted] for [redacted], an increase in [redacted]) were observed, and the drug substance was unstable.

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

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a lyophilized powder for reconstitution for injection. It is available in strengths of 250, 500, 1000, 2000, and 3000 IU/vial. The excipients used are L-histidine, glycine, sucrose, sodium chloride, calcium chloride hydrate, polysorbate 80, and glacial acetic acid. The primary container is a glass vial (10 mL) with [redacted] rubber stopper, and the secondary packaging is a carton.

As an accompanying reconstitution diluent, water for injection (Japanese Pharmacopoeia) 2.5 mL is supplied as a prefilled glass syringe (3 or 5 mL). Jivi is a combination product.

2.2.2 Manufacturing process

The manufacturing process of the drug product consists of drug solution preparation, sterile filtration, filling, freeze-drying, capping, and storage. Sterile filtration, filling, and freeze-drying have been defined as critical steps.

The manufacturing process for the diluent consists of primary filtration, sterile filtration/filling, terminal sterilization, and storage/testing. Sterile filtration/filling and terminal sterilization have been defined as critical steps. Process validation of each commercial-scale manufacturing process has been performed.

2.2.3 Manufacturing process development

During the development of the drug product, changes were made to [redacted] and [redacted], and [redacted] at [redacted] step (change from [redacted] step to [redacted] step), and comparability of quality attributes between pre-change and post-change drug products has been demonstrated.

The drug product produced by the previous manufacturing process was used in a phase I study. The drug product produced by the new manufacturing process was used in phase II/III and phase III studies.

2.2.4 Control of drug product

The proposed specifications for the drug product consist of strength, description, clarity, solubility time, identification ([redacted]), osmolarity, pH, purity ([redacted], [redacted]), moisture content, bacterial endotoxins, uniformity of dosage units, foreign insoluble matter, insoluble particulate matter, sterility, specific activity, and assay (potency [chromogenic substrate assay]).

2.2.5 Stability of drug product

The 250, 500, 1000, 2000, and 3000 IU drug products are formulations of different strengths containing the same concentrations of excipients. For the present application, a bracketing approach to stability was adopted, and only samples on the extremes of strength, i.e. commercial-scale batches of the 250 and 3000 IU drug

products, were tested.

The primary stability studies on the drug product are shown in Table 4.

Table 4. Overview of primary stability studies on drug product

	No. of batches	Storage conditions	Testing period	Storage package
Long-term	250 IU: 3 batches 3000 IU: 3 batches	5 ± 3°C	18 months [a]	Glass vial with [redacted] rubber stopper
Accelerated	250 IU: [redacted] batches 3000 IU: [redacted] batches	30±[redacted]°C [redacted]±[redacted]%RH	6 months	
Stress (temperature)	250 IU: [redacted] batches 3000 IU: [redacted] batches	40±[redacted]°C [redacted]±[redacted]%RH	6 months	
Stress (light)	250 IU: [redacted] batches 3000 IU: [redacted] batches		An overall illumination of 1.2 million lux·h and an integrated near ultraviolet energy of 200 W·h/m^2	Glass vial with [redacted] rubber stopper (with or without carton)
Stability after reconstitution	250 IU: [redacted] batches 3000 IU: [redacted] batches	Room temperature	4 hours	Glass vial with [redacted] rubber stopper

a: ongoing through [redacted] months.

At the long-term and accelerated conditions, no significant changes in quality attributes occurred throughout the testing period, and the batches met the specifications. In the stress testing (temperature), changes in [redacted] (an increase in [redacted]) and a decrease in [redacted] were observed, and the drug product was unstable. In the stress testing (light), a decrease in [redacted] and changes in [redacted] (an increase in [redacted]) were observed, and the drug product was unstable. The post-reconstitution study demonstrated that the potency of the drug product is stable for 4 hours post-reconstitution.

Based on the above, a shelf life of 18 months has been proposed for the drug product when stored in a glass vial, protected from light, at 2°C to 8°C.

2.3 QbD

QbD approaches were used to develop the drug substance, and a quality control strategy was established. The following critical quality attributes (CQAs) were identified from among the quality attributes of the drug substance, including product-related substances, product-related impurities, and process-related impurities. Based on process validation, assessment of consistency of each process, and characterization of multiple batches, process parameters, in-process controls, and specifications were established, and the quality attributes of the drug substance are controlled.

CQAs of the drug substance: potency, protein concentration, purity (aggregates, [redacted], Impurity V), glycosylation variants, oxidation, host cell DNA, HCP, process-related impurities, adventitious agents

2.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the quality of the drug substance and drug product is adequately controlled.

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

The applicant submitted the results from primary pharmacodynamic studies of damoctocog alfa pegol (*in vitro* studies using rabbit, dog, and human plasma, *in vivo* studies in an animal model of hemophilia A, i.e. FVIII-deficient mice (FVIII KO mice) and hemophilia A dogs, etc.) and safety pharmacology studies in rats and rabbits.

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies

3.1.1.1 Effects on clotting in plasma (CTD 4.2.1.1.1)

For assessment of the coagulant activity of damoctocog alfa pegol, rabbit, dog, and human plasma was added with damoctocog alfa pegol or a comparator, Kogenate FS BIO-SET for injection (Kogenate FS), at a final concentration of 0.078 to 10 IU/mL, and activated partial thromboplastin time (aPTT) was measured. There was a trend towards a dose-dependent reduction in the aPTT of rabbit, dog, and human plasma with damoctocog alfa pegol or Kogenate FS.

3.1.2 *In vivo* studies

3.1.2.1 Evaluation of FVIII activity after administration in FVIII KO mice (CTD 4.2.1.1.2)

Following a single intravenous injection of 200 IU/kg damoctocog alfa pegol or Kogenate FS in FVIII KO mice, plasma FVIII activity was measured by chromogenic substrate assay at a total of 8 time points between 5 minutes and 48 hours post-dose (4 males/time point/group). Using the assay results, a pharmacokinetic analysis was performed, and the time taken for plasma FVIII activity to fall to 10 mIU/mL (1% of normal) after administration was compared. As a result, damoctocog alfa pegol (117 hours) tended to exhibit a longer time to the threshold compared to Kogenate FS (68 hours).

3.1.2.2 Evaluation in the tail clip bleeding model of FVIII KO mice (CTD 4.2.1.1.3)

For evaluation of the hemostatic efficacy of damoctocog alfa pegol, FVIII KO mice were intravenously injected with a single dose of 10, 20, 40, 100, or 200 IU/kg damoctocog alfa pegol or Kogenate FS followed by a tail clip 5 minutes post-injection (15 males/group), and the blood loss over 40 minutes following the tail clip was quantified. Then, the dose for normalizing bleeding (defined as blood loss less than the mean + 3 standard deviation [SD] of normal mice [15 males] [352 μL]) in 50% of hemophilia A mice was calculated. As a result, the ED_{50} values of damoctocog alfa pegol and Kogenate FS were approximately 39.0 and approximately 30.3 IU/kg, respectively. The applicant discussed that these results demonstrated comparable hemostatic efficacy between damoctocog alfa pegol and Kogenate FS.

3.1.2.3 Evaluation in the tail vein transection model of FVIII KO mice (CTD 4.2.1.1.4)

For evaluation of the prophylactic efficacy of damoctocog alfa pegol, FVIII KO mice were intravenously injected with a single dose of 4, 12, 24, 40, or 60 IU/kg damoctocog alfa pegol or Kogenate FS, and 48 hours later in the damoctocog alfa pegol group and 24 hours later in the Kogenate FS group, the tail vein was transected (20 males/group). Then survival was assessed for 24 hours after the injury. The doses of damoctocog alfa pegol and Kogenate FS at which 50% of the mice survived were 13.9 and 15.2 IU/kg, respectively. The

applicant discussed that these results demonstrated prolonged prophylactic efficacy of damoctocog alfa pegol vs. Kogenate FS.

3.1.2.4 Evaluation in hemophilia A dogs (CTD 4.2.1.1.6)

Hemophilia A dogs were intravenously injected with a single dose of 50 IU/kg damoctocog alfa pegol or Kogenate FS (2 females or males/group). Plasma FVIII activity was measured by chromogenic substrate assay at a total of 11 time points between 15 minutes and 96 hours post-dose, and the $t_{1/2}$ (mean) was calculated. As a result, the $t_{1/2}$ tended to be longer in the damoctocog alfa pegol group (17.1 hours) than in the Kogenate FS group (3.4 hours). For evaluation of the hemostatic efficacy of damoctocog alfa pegol, the nail was severed 30 minutes before and after administration of each test drug, and the number of blood drops in the subsequent 15 minutes was recorded. As a result, there was a trend towards a reduction in total blood drops after administration in both groups. Whole blood clotting time (WBCT) and thromboelastography (TEG) parameters were determined prior to and 0.5, 24, 48, 72, and 96 hours after treatment with damoctocog alfa pegol or Kogenate FS. As a result, both groups showed improvement in blood clotting after administration, and there was a trend towards prolonged efficacy in the damoctocog alfa pegol group than in the Kogenate FS group.

3.2 Safety pharmacology

The effects of damoctocog alfa pegol on the central nervous, cardiovascular, and respiratory systems, and renal function are shown in Table 5, all of which were assessed in repeated-dose toxicity studies [see Section 5.2].

Table 5. Summary of safety pharmacology studies

Organ systems evaluated	Test system	Endpoints/Method of assessment, etc.	Maximum dosage	Route of administration	Findings	CTD
CNS	Rat (10M/group)	Clinical signs, neurobehavioral function	2250 IU/kg every other day (a total of 7 doses)	Intravenous	No treatment-related effects on CNS	4.2.3.2.1
Cardiovascular system	Rat (10M/group)	Histopathological examination			No treatment-related effects on cardiovascular system	4.2.3.2.1
	Rat (10F/group)					4.2.3.2.2
	Rabbit (6M/group)					4.2.3.2.3
Respiratory system	Rat (10M/group)	Clinical signs, histopathological examination			No treatment-related effects on respiratory system	4.2.3.2.1
	Rat (10F/group)					4.2.3.2.2
Renal function	Rat (10M/group)	Renal function tests			No treatment-related effects on renal function	4.2.3.2.1

3.R Outline of the review conducted by PMDA

PMDA's view:

Based on the results of primary pharmacodynamic studies submitted, damoctocog alfa pegol has the activity of the FVIII molecule, and its hemostatic efficacy *in vivo* is expected. The results of safety pharmacology studies submitted have raised no particular concerns about the safety of damoctocog alfa pegol.

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

The applicant submitted pharmacokinetic data, in the form of the results from studies in rats and rabbits. FVIII activity in plasma samples was measured by chromogenic substrate assay. Following administration of the PEG-60-maleimide-cysteine linker moiety of damoctocog alfa pegol, PEG-60-Mal-Cys (^{14}C-labeled), tissue

radioactivity levels were determined by quantitative and qualitative whole-body autoradiography or liquid scintillation counter.

4.1 Absorption

4.1.1 Single-dose studies

The applicant submitted single-dose pharmacokinetic data, in the form of the results from the following studies in rats and rabbits. The applicant explained that these study results demonstrated the linearity of pharmacokinetics of damoctocog alfa pegol.

4.1.1.1 Single-dose study in rats (CTD 4.2.2.2.1)

Rats (4-13 males/time point/group) were given a single intravenous dose of 60, 250, or 800 IU/kg damoctocog alfa pegol. Plasma FVIII activity was measured at a total of 9 time points between 5 minutes and 32 hours post-dose. Pharmacokinetic parameters are shown in Table 6.

Table 6. Pharmacokinetic parameters in rats (Geometric mean) [a]

No. of animals per time point (n)	Dose (IU/kg)	AUC (IU·h/L)	C_{max} (IU/L)	CL (mL/h/kg)	$t_{1/2}$ (h)	V_{ss} (L/kg)
4-8	60	13200 [b]	1930	4.56 [b]	8.03 [b]	0.0519 [b]
4-13	250	58200	6190	4.30	8.55	0.0531
4-13	800	174000	17100	4.59	8.15	0.0524

a: FVIII activity in plasma samples was measured by chromogenic substrate assay after capture of damoctocog alfa pegol by anti-human FVIII antibodies in order to eliminate the influence of endogenous FVIII in animals. Pharmacokinetic parameters were calculated based on geometric mean FVIII activity at each time point.
b: Estimate (extrapolated part of AUC [from the last quantifiable time to infinity] >20%)

4.1.1.2 Single-dose study in rabbits (CTD 4.2.2.2.3)

Rabbits (9 males/group) were given a single intravenous dose of 25, 100, or 400 IU/kg damoctocog alfa pegol. Plasma FVIII activity was measured at a total of 13 time points (at predose and between 4 minutes and 56 hours post-dose). Pharmacokinetic parameters are shown in Table 7.

Table 7. Pharmacokinetic parameters in rabbits (Geometric mean [Geometric standard deviation]) [a]

No. of animals (n)	Dose (IU/kg)	AUC (IU·h/L)	C_{max} (IU/L)	CL (L/h/kg)	$t_{1/2}$ (h)	V_{ss} (L/kg)
8 [b]	25	7950 [c] (1.45)	494 (1.11)	0.00315 [c] (1.44)	12.6 [c] (1.48)	0.0570 [c] (1.13)
8 [b]	100	29300 [d] (1.19)	2000 (1.15)	0.00341 [d] (1.19)	12.6 [e] (1.21)	0.0618 [d] (1.08)
8 [b]	400	122000 (1.14)	8220 (1.13)	0.00329 (1.14)	11.2 (1.12)	0.0535 (1.16)

a: FVIII activity in plasma samples was measured by chromogenic substrate assay after capture of damoctocog alfa pegol by anti-human FVIII antibodies in order to eliminate the influence of endogenous FVIII in animals.
b: 1 animal with an outlier was excluded.
c: Estimate (extrapolated part of AUC [from the last quantifiable time to infinity] in all animals >20%)
d: Estimate (extrapolated part of AUC [from the last quantifiable time to infinity] in 3 of 8 animals >20%)
e: Estimate (interval used for $t_{1/2}$ calculation < $2 \times t_{1/2}$ in 3 of 8 animals)

4.2 Distribution

As damoctocog alfa pegol is a recombinant FVIII for intravenous administration and considered to distribute primarily into the vascular space, like endogenous FVIII, no distribution studies were conducted with damoctocog alfa pegol. The applicant explained that single-dose studies in rats or rabbits [see Section 4.1.1] showed that the V_{ss} was low in both species, suggesting that damoctocog alfa pegol distributes predominantly

into the vascular space. The distribution of the PEG moiety of damoctocog alfa pegol was evaluated in other pharmacokinetic studies [see Section 4.5.1].

4.3 Metabolism

Damoctocog alfa pegol is a recombinant protein, and no metabolism studies were conducted, in accordance with ICH S6 (R1).

4.4 Excretion

Damoctocog alfa pegol is a recombinant protein, and no excretion studies were conducted in accordance with ICH S6 (R1). The excretion of the PEG moiety of damoctocog alfa pegol was evaluated in other pharmacokinetic studies [see Section 4.5.2].

4.5 Other pharmacokinetic studies

4.5.1 Distribution of PEG-60-Mal-Cys (CTD 4.2.2.7.12)

Rats (1 male/time point) were given a single intravenous dose of ^{14}C-PEG-60-Mal-Cys 11 mg/kg (approximated human lifetime dose of PEG-60 resulting from treatment with damoctocog alfa pegol), and the organ/tissue distribution of radioactivity was determined at a total of 6 time points between 2 hours and 168 days post-dose. In all organs/tissues, radioactivity reached C_{max}, and then declined slowly and continuously until 168 days post-dose while the distribution pattern in organs/tissues remained almost unchanged. At 168 days post-dose, 4.16% of the administered dose was present in the rat body as residual radioactivity, which was distributed primarily in brown adipocytes (0.91% of the dose), skin (0.75% of the dose), and testis (0.73% of the dose), and radioactivity was below the lower limit of detection in blood, brain, and skeletal muscle. The applicant explained that the above results suggested the very low penetration of the blood-brain barrier.

4.5.2 Excretion of PEG-60-Mal-Cys (CTD 4.2.2.7.11)

Following a single intravenous dose of ^{14}C-PEG-60-Mal-Cys 11 mg/kg in rats (3 males/time point), its excretion was determined up to 168 days post-dose (urine up to 231 days post-dose). There was a total recovery of radioactivity of 88.6%, and 68.4%, 13.8%, 5.75%, 0.245% of the administered radioactivity were recovered in the urine, feces, rat body (excluding the gastrointestinal tract), and gastrointestinal tract, respectively. The urine samples were analyzed by high performance liquid chromatography (HPLC), which showed that the majority of radioactivity in urine (74%) was attributable to the unchanged compound (PEG-60-Mal-Cys). Generally, the fate of PEG from a PEGylated protein in the body is similar to that of PEG following administration of PEG alone, and high molecular weight PEGs are considered to be negligibly metabolized (*Drug Discov Today*. 2014; 19: 1623-31, *Drug Metab Dispos*. 2007; 35: 9-16). The applicant discussed that the above results indicated that PEG (molecular weight, 60 kDa) from damoctocog alfa pegol also is mostly excreted without metabolism.

4.R Outline of the review conducted by PMDA

Based on the submitted pharmacokinetic data, PMDA considers that there are no particular problems from a pharmacokinetic perspective. Since damoctocog alfa pegol was suggested to distribute predominantly into the

vascular space, the protein moiety of damoctocog alfa pegol was considered to be metabolized into peptides and amino acids, and its PEG moiety was considered to be excreted without metabolism, PMDA concluded that the omission of distribution, metabolism, and excretion studies of damoctocog alfa pegol based on ICH S6 (R1) is acceptable.

5. Toxicity and Outline of the Review Conducted by PMDA

5.1 Single-dose toxicity

Test system	Route of administration	Dose (IU/kg)	Principal findings	Approximate lethal dose (IU/kg)	Attached document CTD
Male rat (Sprague Dawley [SD])	Intravenous	0,[a] 800, 4000, Kogenate FS (comparator) 4000	No toxic signs with damoctocog alfa pegol or Kogenate FS	>4000	4.2.3.1.1
Male rabbit (New Zealand White [NZW])	Intravenous	0,[a] 400, 4000, Kogenate FS (comparator) 4000	No toxic signs with damoctocog alfa pegol or Kogenate FS	>4000	4.2.3.1.2

a: vehicle

5.2 Repeated-dose toxicity

Test system	Route of administration	Duration of dosing	Dose (IU/kg/injection)	Principal findings	NOAEL (IU/kg/injection)	Attached document CTD
Male rat (SD)	Intravenous	2 weeks (every other day) + 4-week recovery	0,[a] 75, 750, 2250, Kogenate FS (comparator) 2250	No toxic signs with damoctocog alfa pegol or Kogenate FS	2250	4.2.3.2.1
Female rat (SD)	Intravenous	2 weeks (every other day) + 4-week recovery	0,[b] 75, 750, 2250	No toxic signs	2250	4.2.3.2.2
Male rabbit (NZW)	Intravenous	2 weeks (every other day) + 4-week recovery	0,[a] 75, 750, 2250, Kogenate FS (comparator) 2250	No toxic signs except for findings associated with a xenogeneic immune response to the rFVIII molecule (prolonged aPTT, etc.), with damoctocog alfa pegol or Kogenate FS	2250	4.2.3.2.3

a: vehicle
b: saline

5.3 Genotoxicity

No genotoxicity studies have been conducted because rFVIII molecule raises no concern for genotoxicity.

5.4 Carcinogenicity

Since there are no findings suggestive of the carcinogenic potential of rFVIII or PEG, the components of damoctocog alfa pegol, and long-term repeated dosing of damoctocog alfa pegol is not possible due to the formation of neutralizing antibodies, no carcinogenicity studies were conducted.

5.5 Reproductive and developmental toxicity

Since there are no reports suggesting reproductive and developmental adverse events with existing rFVIII products, and toxicity studies of damoctocog alfa pegol in rats or rabbits showed no findings suggestive of effects on the male and female reproductive organs, no reproductive and developmental toxicity studies were conducted.

5.6 Local tolerance

The local tolerance of damoctocog alfa pegol was assessed as part of single-dose and repeated-dose toxicity studies. A single intravenous dose of up to 4000 IU/kg damoctocog alfa pegol, and repeated intravenous doses of up to 2250 IU/kg damoctocog alfa pegol were locally well tolerated.

5.7 Other toxicity studies

5.7.1 Two-week repeated intravenous dose toxicity study in juvenile rats

Test system	Route of administration	Duration of dosing	Dose (IU/kg/injection)	Principal findings	NOAEL (IU/kg/injection)	Attached document CTD
Juvenile male rat (Wistar) Postnatal day 17 or 32	Intravenous	16 days (twice weekly)	0,[a] 200, 1000	No toxic signs	1000	4.2.3.5.4.1

a: vehicle

5.7.2 Immunogenicity in hemophilia A mice

Test system	Route of administration	Duration of dosing	Dose (IU/kg/injection)	Principal findings	Attached document CTD
Male FVIII KO mouse	Intravenous	5 weeks (once weekly)	13, 52, 200, Kogenate FS (comparator) 52, 200	Incidences of binding and neutralizing antibodies were lower with damoctocog alfa pegol than with Kogenate FS.	4.2.3.7.2.1

5.7.3 *In vitro* complement activation in human serum

Type of study	Test method	Principal findings	Attached document CTD
Testing for complement activation *in vitro*	Serum obtained from healthy male volunteers was exposed to 3 or 30 IU/mL damoctocog alfa pegol for 60 minutes at 37°C, and formation of complement factors, C3a and sC5b-9, was measured by enzyme-linked immunosorbent assay (ELISA). As comparators, the excipients of damoctocog alfa pegol, PEG-60-Mal-Cys, and 2 PEGs with different molecular sizes (12 kDa and 108 kDa) were also tested.	There was no increase in C3a or sC5b-9 with any test article. These test articles were considered not to induce complement activation *in vitro*.	4.2.3.7.2.2

5.7.4 *In vitro* tissue cross-reactivity

Type of study	Test method	Principal findings	Attached document CTD
In vitro tissue cross-reactivity study	Binding specificity of damoctocog alfa pegol vs. Kogenate FS to normal human tissues (cerebrum, heart, kidney, liver, lung, spleen) was determined immunohistologically.	Damoctocog alfa pegol and Kogenate FS had comparable specific binding to endothelial cells of the heart, kidney, and lung. It was concluded that there are no differences in tissue cross-reactivity between damoctocog alfa pegol and the existing rFVIII product.	4.2.3.7.2.3

5.7.5 Toxicity studies of PEG-60-Mal-Cys

Single-dose toxicity, repeated-dose toxicity, genotoxicity, and juvenile toxicity studies were conducted with PEG-60-Mal-Cys to evaluate the safety of the PEG-linker component of damoctocog alfa pegol.

5.7.5.1 PEG-60-Mal-Cys: Single-dose toxicity

Test system	Route of administration	Dose (mg/kg)	Principal findings	Approximate lethal dose (mg/kg)	Attached document CTD
Male rat (SD)	Intravenous	0,[a] 23, 70, 210	No toxic signs	>210	4.2.3.7.7.1
Male rabbit (NZW)	Intravenous	0,[a] 2, 20	No toxic signs	>20	4.2.3.7.7.2

a: saline

5.7.5.2 PEG-60-Mal-Cys: Repeated-dose toxicity

Test system	Route of administration	Duration of dosing	Dose (mg/kg/injection)	Principal findings	NOAEL (mg/kg/injection)	Attached document CTD
Male rat (SD)	Intravenous	4 weeks (every other day) + 4-week recovery	0,[a] 0,[b] 0.045, 0.7, 11	No toxic signs	11	4.2.3.7.7.3
Male rabbit (NZW)	Intravenous	4 weeks (twice weekly) + 13-week recovery	0,[a] 0.02, 0.2, 2	No toxic signs	2	4.2.3.7.7.4

a: saline
b: vehicle

5.7.5.3 PEG-60-Mal-Cys: Genotoxicity

Type of study		Test system	Metabolic activation	Doses/concentrations	Test result	Attached document CTD
In vitro	Bacterial reverse mutation assay	*Salmonella typhimurium*: TA98, TA100, TA102, TA1535, TA1537	S9 −/+	0, 100, 250, 500, 1000, 2500, 5000 μg/plate	Negative	4.2.3.7.7.5
	Forward cell mutation assay in cultured mammalian cells	Mouse lymphoma L5178Y cells	S9 − (3 and 24 hours)	0, 150, 500, 1500, 5000 μg/mL	Negative	4.2.3.7.7.6
			S9 + (3 hours)		Negative	
In vivo	Rodent micronucleus test	Male rat (SD) Peripheral blood		0,[a] 0,[b] 0.045, 0.7, 11 mg/kg (intravenous injection, 4 weeks)	Negative	4.2.3.7.7.3

a: saline
b: vehicle

5.7.5.4 PEG-60-Mal-Cys: Repeated-dose toxicity study in juvenile rats

Test system	Route of administration	Duration of dosing	Dose (mg/kg/injection)	Principal findings	NOAEL (mg/kg/injection)	Attached document CTD
Juvenile male rat (Wistar) Postnatal day 17	Intravenous	30 days (twice weekly)	0,[a] 0.4, 2.0	No toxic signs	2.0	4.2.3.7.7.7

a: saline

5.R Outline of the review conducted by PMDA

The applicant's explanation about the safety of the PEG moiety of damoctocog alfa pegol:

It has been suggested that administration of PEGylated pharmaceuticals may induce vacuolation in the renal tubular epithelium, the choroid plexus epithelium, etc., and the occurrence of these findings depends on

PEG molecular weight, duration of treatment, the cumulative PEG dose, etc. (*Toxicol Pathol.* 2015; 43: 959-83, etc.). Although the use of damoctocog alfa pegol poses a risk in terms of administering a relatively large 60 kDa PEG over a long period of time, given that the cumulative dose itself is low (treatment with damoctocog alfa pegol 60 IU/kg [approximately 4 μg/kg of PEG] twice weekly results in a cumulative PEG dose of approximately 32 μg/kg/month), tissue vacuolation and associated toxicological changes related to PEG accumulation are unlikely to occur.

The applicant discussed with [redacted], and in addition to studies with PEG-60-Mal-Cys, a 26-week toxicity study of damoctocog alfa pegol in immune-deficient rats to characterize the PEG distribution/accumulation profile following administration of damoctocog alfa pegol is ongoing. In this study, immune-deficient Rowett nude male rats were intravenously injected with 0, 40, 400, or 1200 IU/kg/injection of damoctocog alfa pegol twice weekly for 13 weeks (n = 10/group), 26 weeks (n = 20/group), or 26 weeks followed by a 26-week recovery (n = 15/group). Based on the data through 26 weeks of treatment, dose-proportional increases in PEG exposure were observed, whereas there was no sign of PEG accumulation in the brain (including the choroid plexus), kidneys, spleen, etc. in the 1200 IU/kg/injection group, and the presence of PEG was not detected by immunohistological staining, either. The no-observed-adverse-effect-level (NOAEL) was determined to be 1200 IU/kg/injection.

PMDA concluded that the above explanation by the applicant is acceptable and that the risk associated with PEG accumulation from the use of damoctocog alfa pegol is unlikely to arise. In clinical studies of damoctocog alfa pegol (Study 13024 and Study 15912), the plasma PEG concentrations after administration of damoctocog alfa pegol were below the lower limit of quantification (0.1 mg/L), and there was also no indication of PEG accumulation with long-term administration of damoctocog alfa pegol.

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

6.1 Summary of biopharmaceutic studies and associated analytical methods

Plasma FVIII activity was measured by chromogenic substrate assay. In Study 13401 and Study 13024, one-stage clotting assay was also used, which produced similar results to chromogenic substrate assay. Although a clinical pharmacology study of damoctocog alfa pegol demonstrated that plasma FVIII activity following administration of damoctocog alfa pegol can be measured appropriately by one-stage clotting assay, when commercially available assay reagents (aPTT reagents) were tested, some aPTT reagents were shown to underestimate or overestimate the FVIII activity. The applicant explained that the package insert etc. will advise that an appropriate reagent should be selected to measure plasma FVIII activity after administration of damoctocog alfa pegol.

6.2 Clinical pharmacology

The applicant submitted clinical pharmacology evaluation data, in the form of the results from a foreign phase I study (CTD 5.3.3.2.1, Study 13401), a global phase II/III study (CTD 5.3.5.2.1, Study 13024), and a foreign phase III study (CTD 5.3.5.2.5, Study 15912). The results of a population pharmacokinetic analysis using the

data obtained from these studies (CTD 5.3.3.5.1) were also submitted.

6.2.1 Patient studies

6.2.1.1 Foreign phase I study (CTD 5.3.3.2.1, Study 13401; Study period, October 2010 to October 2011)

The pharmacokinetics of damoctocog alfa pegol were evaluated in 14 patients with severe hemophilia A (FVIII activity <1%) aged between 18 and 65 years who had been previously treated for ≥150 exposure days with any FVIII concentrate and had no history or current evidence of inhibitors (7 per cohort). Subjects received a single intravenous dose of 25 IU/kg (low dose cohort) or 50 IU/kg (high dose cohort) Kogenate FS, and plasma FVIII activity was measured at a total of 9 time points (at pre-dose and between 15 minutes and 48 hours post-dose). After a ≥3-day washout, subjects received a single intravenous dose of 25 IU/kg (low dose cohort) or 60 IU/kg (high dose cohort) damoctocog alfa pegol, and plasma FVIII activity was measured at a total of 12 time points (at pre-dose and between 15 minutes and 168 hours post-dose). The pharmacokinetic parameters of Kogenate FS and damoctocog alfa pegol are shown in Table 8. The applicant explained that damoctocog alfa pegol has a longer $t_{1/2}$ than Kogenate FS, and that the AUC and C_{max} of damoctocog alfa pegol increased almost dose-proportionally between the doses of 25 and 60 IU/kg.

Table 8. Pharmacokinetic parameters of Kogenate FS and damoctocog alfa pegol (Mean ± SD) [a]

	Low dose cohort (N = 7)		High dose cohort (N = 7)	
	Kogenate FS 25 IU/kg [b]	Damoctocog alfa pegol 25 IU/kg	Kogenate FS 50 IU/kg	Damoctocog alfa pegol 60 IU/kg
AUC (IU·h/dL)	1210 ± 553	1640 ± 550	2650 ± 1080	4550 ± 1810
C_{max} (IU/dL)	71.8 ± 17.6	64.3 ± 9.2	238 ± 76	177 ± 45
$t_{1/2}$ (h)	13.4 ± 3.8	18.6 ± 4.6	13.2 ± 2.1	18.7 ± 2.9
MRT (h)	19.2 ± 5.4	26.7 ± 6.6	18.0 ± 3.3	27.7 ± 4.5
CL (dL/h/kg)	0.0247 ± 0.0116	0.0168 ± 0.0039	0.0210 ± 0.0065	0.0144 ± 0.0037
V_{ss} (dL/kg)	0.433 ± 0.134	0.428 ± 0.050	0.365 ± 0.090	0.386 ± 0.066

a: Plasma FVIII activity was measured by chromogenic substrate assay.
b: The parameters other than C_{max} are based on N = 6; 1 subject was excluded because the parameters other than C_{max} could not be evaluated appropriately due to insufficient sampling times.

After 168 hours following a single dose of damoctocog alfa pegol, subjects in the low dose cohort received 25 IU/kg damoctocog alfa pegol twice weekly for 8 weeks (a total of 16 doses), and subjects in the high dose cohort received 60 IU/kg damoctocog alfa pegol once weekly for 8 weeks (a total of 9 doses). Plasma FVIII activity was measured at a total of 12 time points (before the last dose and between 15 minutes and 168 hours after the last dose), and the pharmacokinetics of damoctocog alfa pegol were determined. As a result, multiple dosing did not alter the pharmacokinetic profile of damoctocog alfa pegol.

6.2.1.2 Global phase II/III study (CTD 5.3.5.2.1, Study 13024; Study period, April 2012 to December 2013)

The pharmacokinetics of damoctocog alfa pegol were evaluated in 22 patients with severe hemophilia A (FVIII activity <1%) aged between 12 and 65 years who had been previously treated for ≥150 exposure days with any FVIII concentrate and had no history or current evidence of inhibitors (including 4 Japanese subjects). Following a single intravenous dose of 60 IU/kg damoctocog alfa pegol, plasma FVIII activity was measured at ≥10 time points (at pre-dose and between 15 minutes and 96 hours post-dose). Pharmacokinetic parameters

are shown in Table 9.

The applicant explained that there were no apparent differences in the pharmacokinetic parameters between subjects aged ≥12 and <18 years and subjects aged ≥18 years and also between Japanese and non-Japanese subjects aged ≥18 years.

Table 9. Pharmacokinetic parameters following a single dose of 60 IU/kg damoctocog alfa pegol (Mean ± SD) [a]

	12-17 years	18-65 years		
		Japanese subjects	Non-Japanese subjects	Overall population
	N = 3 [b]	N = 4	N = 15	N = 19
AUC (IU·h/dL)	4010 ± 1090	3250 ± 565	4050 ± 1440	3880 ± 1330
C_{max} (IU/dL)	165 ± 29	157 ± 28	167 ± 23	164 ± 24
$t_{1/2}$ (h)	17.9 ± 1.7	16.5 ± 3.3	17.8 ± 4.9	17.6 ± 4.6
MRT (h)	25.3 ± 0.7	23.6 ± 5.7	25.7 ± 7.0	25.2 ± 6.7
CL (dL/h/kg)	0.0157 ± 0.0040	0.0185 ± 0.0030	0.0166 ± 0.0064	0.0170 ± 0.0058
V_{ss} (dL/kg)	0.399 ± 0.107	0.425 ± 0.035	0.388 ± 0.062	0.396 ± 0.058

a: Plasma FVIII activity was measured by chromogenic substrate assay.
b: All non-Japanese subjects

Of 22 subjects who completed single-dose pharmacokinetic evaluation, the multiple-dose pharmacokinetic was also evaluated in 16 subjects (including no Japanese subjects) after ≥3 months of treatment with damoctocog alfa pegol. The dose used for PK evaluation was 60 IU/kg. As a result, multiple dosing of damoctocog alfa pegol did not alter its pharmacokinetic profile.

6.2.1.3 Foreign phase III study (CTD 5.3.5.2.5, Study 15912; Study period, May 2013 to March 2015)

The pharmacokinetics of damoctocog alfa pegol were evaluated in 34 patients with hemophilia A (FVIII activity <1%) aged <12 years (<6 years, 16 subjects; ≥6 and <12 years, 18 subjects) who had been previously treated for >50 exposure days with any FVIII concentrate and had no history or current evidence of inhibitors. Following a single intravenous dose of 60 IU/kg damoctocog alfa pegol, plasma FVIII activity was measured at ≥4 time points (at pre-dose and between 20-30 minutes and 72 hours post-dose). Pharmacokinetic parameters are shown in Table 10.

The applicant explained that there was a trend towards higher CL and lower AUC in subjects aged <6 years than in subjects aged ≥6 and <12 years. There was a trend towards higher CL and lower AUC in subjects aged <12 years in this study than in subjects aged ≥12 years in Studies 13401 and 13024 [see Table 8 and Table 9].

Table 10. Pharmacokinetic parameters in subjects aged <12 years (Mean ± SD) [a]

	<6 years (N = 14 [b])	≥6 and <12 years (N = 13 [c])
AUC (IU·h/dL)	2210 ± 735	2880 ± 525
C_{max} (IU/dL)	119 ± 21	129 ± 24 [d]
$t_{1/2}$ (h)	15.0 ± 4.1	16.0 ± 3.5 [e]
MRT (h)	20.5 ± 5.5	24.0 ± 5.7
CL (dL/h/kg)	0.0314 ± 0.0141	0.0214 ± 0.0042
V_{ss} (dL/kg)	0.595 ± 0.164	0.501 ± 0.095

a: Plasma FVIII activity was measured by chromogenic substrate assay.
b: Excluding 1 subject with dose deviation and 1 subject with an outlier (low exposure).
c: Excluding 1 subject with dose deviation, 2 subjects in whom $t_{1/2}$ was the only evaluable parameter, and 2 subjects in whom C_{max} was the only evaluable parameter.
d: Including 2 subjects in whom C_{max} was the only evaluable parameter.
e: Including 2 subjects in whom $t_{1/2}$ was the only evaluable parameter.

6.2.1.4 Population pharmacokinetic analysis (CTD 5.3.3.5.1)

Using plasma FVIII activity data (by chromogenic substrate assay) (a total of 2224 sampling points) from a foreign phase I study (Study 13401), a global phase II/III study (Study 13024), and a foreign phase III study (Study 15912), a population pharmacokinetic analysis was performed using NONMEM (version 7.2). The base model for this analysis was a 1-compartment model, and age, height, body weight, body mass index (BMI), lean body mass (LBM), and vWF at baseline and race were evaluated as covariates. As a result, the final model selected was a 1-compartment model with LBM as a covariate on CL and V_c and vWF as a covariate on CL. Simulations using this model predicted that following a single dose of 60 IU/kg damoctocog alfa pegol in patients with hemophilia A aged ≥12 years, plasma FVIII level at ≥1 IU/dL is maintained for a median of 127.2 hours (95th percentile, 192.3 hours). The applicant explained that a maintenance of plasma FVIII level at ≥1 IU/dL for ≥5 days for approximately 50% of patients and for ≥7 days for some patients was suggested.

6.R Outline of the review conducted by PMDA

Based on the submitted clinical pharmacology data, PMDA considers that damoctocog alfa pegol was shown to have a longer half-life than the existing unmodified FVIII product. The appropriateness of the prophylactic regimen will be discussed in Section 7.R.5 because the dosing regimens selected for clinical studies and the efficacy results should also be discussed.

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

The applicant submitted efficacy and safety evaluation data, in the form of the results from a foreign phase I study (CTD 5.3.3.2.1, Study 13401), a global phase II/III study (CTD 5.3.5.2.1, Study 13024), and a foreign phase III study (CTD 5.3.5.2.5, Study 15912). Listing of clinical studies is shown in Table 11.

Table 11. Listing of clinical studies [a]

Geographical location	Study identifier	Phase	Study population	No. of subjects treated	Dosing regimen	Main endpoints
Foreign	13401	I	Previously treated patients with severe hemophilia A (≥18 and ≤65 years)	14 subjects (7/cohort)	Low dose cohort: A single dose of 25 IU/kg Kogenate FS followed by a ≥3-day washout and a single dose of 25 IU/kg damoctocog alfa pegol. Then 25 IU/kg damoctocog alfa pegol twice weekly for 8 weeks. High dose cohort: A single dose of 50 IU/kg Kogenate FS followed by a ≥3-day washout and a single dose of 60 IU/kg damoctocog alfa pegol. Then 60 IU/kg damoctocog alfa pegol once weekly for 8 weeks.	Safety PK
Global	13024	II/III	Previously treated patients with severe hemophilia A (≥12 and ≤65 years)	Part A: 134 subjects · On-demand group: 20 subjects · Prophylaxis group: 114 subjects	On-demand group: The dose as indicated based on the location and severity of bleeds (up to 60 IU/kg per infusion). 36 weeks of duration Prophylaxis group: (first 10 weeks) 25 IU/kg damoctocog alfa pegol twice weekly (Weeks 10-36) · For subjects with ≥2 breakthrough (joint/muscle) bleeds during the first 10 weeks of treatment, 30-40 IU/kg twice weekly · For subjects with <2 breakthrough bleeds during the first 10 weeks of treatment, randomization to an every 5-day (initially 45 IU/kg, up to 60 IU/kg) or every 7-day (a fixed dose of 60 IU/kg) regimen.	Safety Efficacy PK
				Part B: 16 subjects	Subjects were treated according to the type of procedure, using doses expected to maintain therapeutic levels of FVIII activity, for up to 3 weeks.	Safety Efficacy
Foreign	15912	III	Previously treated patients with severe hemophilia A (≥0 and <12 years)	61 subjects (<6 years, 32 subjects; ≥6 and <12 years, 29 subjects)	25-60 IU/kg twice weekly, 45-60 IU/kg every 5 days, or 60 IU/kg every 7 days, at the discretion of the investigator, for ≥50 exposure days and ≥6 months.	Safety Efficacy PK

a: For Study 13024 and Study 15912, the information on the main study is presented.

The clinical studies are summarized below. The pharmacokinetic results from these studies are described in Section "6.2 Clinical pharmacology."

7.1 Phase I studies

7.1.1 Foreign phase I study (CTD 5.3.3.2.1, Study 13401; Study period, October 2010 to October 2011)

A study was conducted in patients with severe hemophilia A (FVIII activity <1%) aged between 18 and 65 years who had been previously treated for ≥150 exposure days with any FVIII concentrate and had no history or current evidence of inhibitors (target sample size, 12-16 subjects) at 4 sites in the US to evaluate the safety and pharmacokinetics of damoctocog alfa pegol.

The study included 2 cohorts (high dose and low dose cohorts), and the dosing regimen is shown below.

Low dose cohort: A single dose of 25 IU/kg Kogenate FS followed by a ≥3-day washout and a single dose of 25 IU/kg damoctocog alfa pegol. Multiple dosing of damoctocog alfa pegol (25 IU/kg twice weekly) began 7 days after the first dose of damoctocog alfa pegol and continued for 8 weeks (a total of 16 doses).

High dose cohort: A single dose of 50 IU/kg Kogenate FS followed by a ≥3-day washout and a single dose of 60 IU/kg damoctocog alfa pegol. Multiple dosing of damoctocog alfa pegol (60 IU/kg once weekly) began 7 days after the first dose of damoctocog alfa pegol and continued for 8 weeks (a total of 9 doses).

Among 15 subjects enrolled in the study, 14 subjects (7 in each cohort) who received study drug were included in the safety analysis population.

Regarding safety, 28.6% (4 of 14) of subjects experienced 8 adverse events (low dose cohort, diarrhoea, nausea, vomiting, arthralgia, pain in extremity, headache, and pelvic haemorrhage [n = 1 each]; high dose cohort, toothache [n = 1]) through 30 days after the last dose of damoctocog alfa pegol, and the outcomes of these events were all reported as resolved. Among these events, 1 event reported by 1 subject in the low dose cohort (pain in extremity) occurred between after administration of Kogenate FS and the start of treatment with damoctocog alfa pegol. Although 1 serious adverse event occurred in 1 subject in the low dose cohort (pelvic haemorrhage), its causal relationship to damoctocog alfa pegol was denied and its outcome was reported as resolved.

There were no adverse drug reactions, deaths, or adverse events leading to treatment discontinuation during the study period.

7.2 Phase II/III studies

7.2.1 Global phase II/III study (CTD 5.3.5.2.1, Study 13024 (main study); Study period, April 2012 to June 2014)

An open-label study was conducted in patients with severe hemophilia A (FVIII activity <1%) aged between 12 and 65 years who had been previously treated for ≥150 exposure days with any FVIII concentrate and had no history or current evidence of inhibitors (target sample size, 120-140 subjects in Part A [20 in the on-demand group, 100-120 in the prophylaxis group], ≥10 subjects in Part B) at 60 sites in 20 countries including Japan to evaluate the safety, efficacy, and pharmacokinetics of damoctocog alfa pegol. The study was divided into 2 parts: Part A (to evaluate the safety, efficacy, and pharmacokinetics of damoctocog alfa pegol for on-demand treatment and routine prophylaxis) and Part B (to evaluate the safety and efficacy of damoctocog alfa pegol for perioperative management [major surgery]). The study design is described below.

Part A: Subjects were assigned to their preferred treatment, i.e. on-demand treatment or prophylactic treatment. Subjects in the on-demand group were to receive damoctocog alfa pegol as needed to control bleeding episodes, and the duration of treatment was 36 weeks. On the other hand, subjects in the prophylaxis group started treatment with twice weekly infusions of damoctocog alfa pegol at a dose of 25 IU/kg for 10 weeks (the run-in phase), and were to be assigned/randomized to different regimens specified in Table 12, based on the number of breakthrough bleeds during the 10-week run-in phase, and treated with damoctocog alfa pegol for 26 weeks. Subjects in the prophylaxis group who experienced <2 breakthrough bleeds during the run-in phase were to be randomized to the every 5- or 7-day treatment group until the number in each group reached 40. After that, the remaining subjects were to be enrolled in the twice weekly forced group. Subjects in the prophylaxis group were also allowed to use damoctocog alfa pegol as needed for any bleeding episodes. The dosage required to treat bleeding events was determined, according to the type, location, and severity of the bleeding

event, based on each subject's prior experience with treatment of bleeding events, the treating physician's recommendations, World Federation of Hemophilia (WFH)'s guidelines, etc. The maximum dose was 60 IU/kg.

Table 12. Prophylactic regimens

No. of breakthrough bleeds during the 10-week period	Group	Dosing regimen
≥2	Twice weekly failed group	30-40 IU/kg twice weekly
<2	Every 5-day treatment group [a]	45-60 IU/kg every 5 days
	Every 7-day treatment group [a]	60 IU/kg every 7 days
	Twice weekly forced group	30-40 IU/kg twice weekly

a: Subjects in the every 5- or 7-day treatment group who experienced an unacceptable increase in bleeding frequency had the option of a one-time change in dosing frequency. A subject who had the one-time change in dosing frequency was regarded as rescued (The data after the change in dosing frequency were not used as data from the every 5- or 7-day treatment group).

Part B: Subjects were to receive a loading dose of 50 IU/kg damoctocog alfa pegol or a dose determined by individual pharmacokinetic data within 60 minutes before start of procedure, followed by 15 to 50 IU/kg to be repeated as indicated. Subjects undergoing major surgery were to receive damoctocog alfa pegol for pre-surgical pharmacokinetic measurements followed by treatment with the study drug during their hospital stay and up to the time of discharge, for a period not exceeding a total of 3 weeks.

In Part A, all of 134 subjects who were enrolled in the study and received at least 1 dose of damoctocog alfa pegol (20 in the on-demand group [including 1 Japanese subject], 114 in the prophylaxis group [including 10 Japanese subjects]) were included in the safety analysis population. After excluding 2 subjects in the prophylaxis group who had no evaluable efficacy data (these subjects were discontinued from the study due to the occurrence of an adverse event after the first dose of damoctocog alfa pegol or consent withdrawal), 132 subjects (20 in the on-demand group, 112 in the prophylaxis group) were included in the intent-to-treat (ITT) population, which was used as the primary efficacy analysis population. Among the 112 subjects in the prophylaxis group, 110 subjects excluding 2 subjects who were discontinued from the study during the run-in phase, were enrolled in the twice weekly failed, every 5-day treatment, every 7-day treatment, or twice weekly forced group (13 subjects, 43 subjects, 43 subjects, or 11 subjects, respectively) (including 0, 4, 5, or 1 Japanese subjects, respectively).

In Part B, all of 16 subjects who were enrolled in the study and received at least 1 dose of damoctocog alfa pegol (no Japanese subjects) (1 subject who received 1 dose of damoctocog alfa pegol for pre-surgical pharmacokinetic measurements, dropped out of the study without undergoing surgery, was re-screened, and entered Part B again was counted as 2 subjects) were included in the safety analysis population. After excluding 2 subjects who did not undergo surgery, 14 subjects were included in the ITT population, which was used as the primary efficacy analysis population.

In Part A, the number of exposure days to damoctocog alfa pegol per subject (mean ± SD) was 32.4 ± 19.3 [range, 9-75] days in the on-demand group and 60.4 ± 14.0 [range, 4-99] days in the prophylaxis group in the ITT population.

The primary endpoint was the responder rate (responders defined as subjects with an ABR [annualized number

of bleeds] of <9 bleeds per year who did not increase their dosing frequency or drop out), and the responder rates in the on-demand and prophylaxis groups are shown in Table 13. The responder rates among Japanese subjects were 0% (0 of 1 subject) in the on-demand group and 80.0% (8 of 10 subjects) in the prophylaxis group.

Table 13. Responder rates in prophylaxis and on-demand groups (ITT)

	On-demand	Prophylaxis
No. of subjects (N)	20	112
No. of responders (%)	1 (5.0)	85 (75.9)
Between-group difference [two-sided 95% CI]	70.89 [48.78, 88.11]	
P-value [a]	<0.0001	

a: Fisher's exact test (One-sided level of significance of 0.025)

The ABRs in the on-demand and prophylaxis groups are shown in Table 14. Among Japanese subjects, the median ABRs [range] were 37.27 in the on-demand group (1 subject) and 2.85 [0.0, 7.4] in the prophylaxis group (10 subjects).

Table 14. ABR (bleeds per year) in Weeks 0-36 (ITT)

		On-demand (N = 20)	Prophylaxis (N = 112)
No. of subjects with a bleed requiring treatment		20	75
No. of bleeds treated		386	316
ABR (bleeds per year)	Mean ± SD	28.60 ± 17.97	4.10 ± 4.73
	Median [Range]	23.42 [7.3, 83.2]	2.82 [0.0, 23.4]

The ABRs by prophylactic regimen are shown in Table 15. Among Japanese subjects, the median ABRs [range] in Weeks 10 to 36 were 6.01 [2.1, 10.4] in the every 5-day treatment group (4 subjects), 6.33 [0, 25.7] in the every 7-day treatment group (5 subjects), and 0.00 in the twice weekly forced group (1 subject).

Table 15. ABRs (bleeds per year) by prophylactic regimen (ITT)

		Twice weekly failed group (N = 13)	Every 5-day treatment group (N = 43)	Every 7-day treatment group (N = 43)	Twice weekly forced group (N = 11)
Weeks 0-10	Mean ± SD	19.01 ± 6.84	1.48 ± 2.73	2.42 ± 3.63	2.71 ± 3.49
	Median [Range]	17.40 [9.9, 30.0]	0.00 [0.0, 10.0]	0.00 [0.0, 15.7]	0.00 [0.0, 10.4]
Weeks 10-36	Mean ± SD	7.24 ± 7.50	3.30 ± 4.26	6.43 ± 10.04	2.21 ± 2.72
	Median [Range]	4.11 [0.0, 26.1]	1.93 [0.0, 16.1]	3.85 [0.0, 53.1]	1.93 [0.0, 7.7]

Regarding the efficacy of damoctocog alfa pegol in the treatment of bleeding events, the treatment response was assessed as per Table 16 and Table 17. Response to treatment of bleeds was rated as "excellent" or "good" for 72.4% (508 of 702) of bleeds. Among Japanese subjects, this proportion was 38.0% (19 of 50 bleeds). After excluding 9 bleeds with missing assessment, this proportion was 73.3% (508 of 693 bleeds).

Table 16. Subject assessment of response to treatment of a bleed

Rating	Definition
Excellent	Abrupt pain relief and/or improvement in signs of bleeding with no additional infusion administered
Good	Definite pain relief and/or improvement in signs of bleeding, but possibly requiring more than one infusion for complete resolution
Moderate	Probable or slight improvement, with at least one additional infusion for complete resolution
Poor	No improvement or condition worsened.

Table 17. Investigator assessment of response to treatment of a major bleed

Rating	Definition
Excellent	As good or better than other FVIII concentrates
Good	At least as good as other FVIII concentrates
Moderate	Less than optimal for the type of bleeding, but no need to change therapeutic regimen
Poor	Inadequate therapeutic response, change in therapeutic regimen required

Regarding the efficacy of damoctocog alfa pegol during surgery, the adequacy of hemostasis during and after minor surgeries performed in Part A and major surgeries performed in Part B was assessed using a 4-point scale presented in Table 18.

Table 18. Perioperative rating scale [a]

Rating	Intra-operative	Post-surgical
Excellent	Blood loss less than expected	As good or better than other FVIII concentrates
Good	Blood loss as expected	At least as good as other FVIII concentrates
Moderate	Blood loss more than expected	Less than optimal, but no need to change therapeutic regimen
Poor	Uncontrolled bleeding	Breakthrough bleeding due to inadequate therapeutic response, change in therapeutic regimen required

a: Intra-operative hemostasis was assessed by the surgeon or the investigator (sub-investigator), and post-operative hemostasis was assessed by the surgeon.

In Part B, 14 subjects underwent 17 major surgeries (knee arthroplasty [n = 5], dental operation [n = 2], synovectomy [n = 2], lower-limb arthroplasty, evacuation of hematoma, hernia repair, hip arthroplasty, limb surgery, penile prosthesis, shoulder rotator cuff repair, and tooth extraction [n = 1 each]). In Part A, 10 subjects underwent 14 minor surgeries (tooth extraction [n = 3], artificial crown procedure [n =2], dental cleaning [n = 2], cataract surgery, colonoscopy, diagnostic aspiration, surgery, tooth repair, vasectomy, and wisdom teeth removal [n = 1 each]). The adequacy of hemostasis during and after surgery was rated as "excellent" or "good" in 100% (17 of 17) and 76.5% (13 of 17) of major surgeries, respectively. The adequacy of hemostasis during and after surgery was rated as "excellent" or "good" in 92.9% (13 of 14) and 71.4% (10 of 14) of minor surgeries, respectively.

Regarding safety, between the first dose and 7 days after the last dose of damoctocog alfa pegol, 74.6% (100 of 134) of subjects experienced 381 adverse events in Part A and 75.0% (12 of 16) of subjects experienced 39 adverse events in Part B. Adverse events reported by ≥5 subjects in Part A are shown in Table 19.

Table 19. Adverse events reported by ≥5 subjects in Part A (Safety analysis population)

	On-demand (N = 20)		Prophylaxis (N = 114)	
Adverse event term	No. of subjects with event (%)	No. of events (n)	No. of subjects with event (%)	No. of events (n)
Nasopharyngitis	2 (10.0)	3	22 (19.3)	31
Headache	1 (5.0)	1	15 (13.2)	27
Arthralgia	1 (5.0)	1	9 (7.9)	11
Back pain	0	0	8 (7.0)	10
Cough	2 (10.0)	3	6 (5.3)	8
Epistaxis	0	0	8 (7.0)	10
Nausea	1 (5.0)	1	4 (3.5)	5
Influenza	0	0	5 (4.4)	9
Ligament sprain	1 (5.0)	1	4 (3.5)	6

In Part B, adverse events reported by ≥2 subjects were procedural haemorrhage (3 subjects, 3 events), procedural pain (3 subjects, 4 events), haemoglobin decreased (3 subjects, 3 events), anti factor VIII antibody positive (2 subjects, 2 events), pyrexia (2 subjects, 2 events), and haematoma (2 subjects, 3 events).

In Part A, 12 subjects experienced 23 adverse drug reactions (headache [n = 4], pruritus [n = 3], palpitations [n = 2], abdominal pain, dry mouth, vessel puncture site pruritus, drug hypersensitivity, hypersensitivity, overdose, alanine aminotransferase increased, arthralgia, musculoskeletal discomfort, dizziness, sensory disturbance, insomnia, thinking abnormal, and dyspnoea [n = 1 each]). In Part B, 3 subjects experienced 8 adverse drug reactions (anti factor VIII antibody positive [n = 2], haematoma [n = 2], tachycardia, drug hypersensitivity, haemoglobin decreased, and haemorrhage subcutaneous [n = 1 each]). The outcome was reported as resolved for all those events, except that the outcomes of thinking abnormal and arthralgia in Part A and anti factor VIII antibody positive [n = 1] in Part B were reported as unresolved. No deaths were reported during the study period.

In Part A, 4 subjects experienced 6 serious adverse events in the on-demand group (alcohol poisoning, pneumonia, device related infection, colonoscopy, knee arthroplasty, and pancreatitis acute [n = 1 each]), and 9 subjects experienced 10 serious adverse events in the prophylaxis group (drug hypersensitivity, tendon rupture, device malfunction, bile duct stone, haemarthrosis, gastroenteritis, injury, arthropathy, overdose, and haemophilic arthropathy [n = 1 each]). In Part B, 2 subjects experienced 3 serious adverse events (anti factor VIII antibody positive [n = 2], haematoma [n = 1]). A causal relationship to damoctocog alfa pegol could not be ruled out for 2 events (drug hypersensitivity, overdose) in Part A and 3 events (anti factor VIII antibody positive [n = 2], haematoma [n = 1]) in Part B. The outcome was reported as resolved for all those events, except that the outcome of 1 event of anti factor VIII antibody positive in Part B was reported as unresolved. In Part A, 2 subjects experienced 2 adverse events leading to study discontinuation (hypersensitivity, drug hypersensitivity). In Part B, 1 subject experienced 2 adverse events leading to study discontinuation (anti factor VIII antibody positive, haematoma).

Regarding safety in Japanese subjects, 54.5% (6 of 11) of subjects experienced 21 adverse events. One subject experienced 2 adverse drug reactions of palpitations, and their outcomes were reported as resolved. Although 2 subjects in the prophylaxis group experienced 2 serious adverse events (bile duct stone, haemarthrosis), their causal relationship to study drug was denied, and the outcomes of those events were reported as resolved. There were no adverse events leading to study discontinuation.

7.3 Phase III studies

7.3.1 Foreign phase III study (CTD 5.3.5.2.5, Study 15912 (main study); Study period, May 2013 to March 2015)

An uncontrolled study was conducted in patients with severe hemophilia A (FVIII activity <1%) aged <12 years who had been previously treated for >50 exposure days with any FVIII concentrate and had no history or current evidence of inhibitors (target sample size, 50 subjects [25 each, <6 years of age and ≥6 and <12 years of age]) at 31 sites in 13 foreign countries to evaluate the safety, efficacy, and pharmacokinetics of damoctocog alfa pegol.

The prophylactic dosing regimen of 25 to 60 IU/kg damoctocog alfa pegol twice weekly, 45 to 60 IU/kg every

5 days, or 60 IU/kg every 7 days was assigned according to the clinical needs of each subject, based on the level of physical activity, a history of bleeding episodes, etc. Any subject who experienced ≥2 breakthrough bleeds within any consecutive 3-month period was allowed to change the dosing frequency. The duration of treatment was ≥6 months and ≥50 exposure days. If a bleed occurred, the subject was to receive damoctocog alfa pegol at a dose up to 60 IU/kg, according to the type, location, and severity of the bleed. Subjects requiring minor surgery were to receive damoctocog alfa pegol before surgery and an additional infusion 24 to 48 hours later as indicated. Also after that, additional dosing was to be considered, according to the subject's condition.

All of 61 subjects who were enrolled in the study and received at least 1 dose of damoctocog alfa pegol (<6 years, 32 subjects; ≥6 and <12 years, 29 subjects) were included in the safety analysis population. After excluding 1 subject who had no evaluable efficacy data (the subject was discontinued from the study due to the occurrence of an adverse event of hypersensitivity after the first dose of damoctocog alfa pegol), 60 subjects (<6 years, 32 subjects; ≥6 and <12 years, 28 subjects) were included in the ITT population, which was used as the primary efficacy analysis population.

In the ITT population, the number of exposure days to damoctocog alfa pegol per subject (mean ± SD) was 50.0 ± 17.0 days [range, 3-68]. There were 53 subjects achieving ≥50 exposure days (<6 years, 25 subjects; ≥6 and <12 years, 28 subjects).

The primary endpoint was the ABR, and response to treatment of bleeds was assessed as per Table 16. The median ABR [range] was 2.87 [0.0, 74.6]. Response to treatment of bleeds was rated as "excellent" or "good" for 85.7% (120 of 140) of bleeds.

Regarding safety, 82.0% (50 of 61) of subjects experienced 285 adverse events between the first dose and 7 days after the last dose of damoctocog alfa pegol. Adverse events reported by ≥5 subjects are shown in Table 20.

Table 20. Adverse events reported by ≥5 subjects (Safety analysis population, N = 61)

Adverse event term	No. of subjects with event (%)	No. of events (n)
Pyrexia	9 (14.8)	13
Contusion	8 (13.1)	8
Headache	8 (13.1)	11
Upper respiratory tract infection	7 (11.5)	7
Epistaxis	7 (11.5)	14
Diarrhoea	6 (9.8)	6
Nasopharyngitis	6 (9.8)	9
Pain in extremity	6 (9.8)	7
Cough	6 (9.8)	6
Oropharyngeal pain	6 (9.8)	6
Vomiting	5 (8.2)	5
Gastroenteritis	5 (8.2)	6

Nine subjects experienced 16 adverse drug reactions (drug specific antibody present [n = 5], hypersensitivity [n = 2], spontaneous haematoma [n = 2], spontaneous haemorrhage, drug hypersensitivity, contusion, subcutaneous haematoma, anti factor VIII antibody positive, dysgeusia, and epistaxis [n = 1 each]). The

outcome was reported as resolved for all those events, except for dysgeusia.

Eleven subjects experienced 22 serious adverse events (drug specific antibody present [n = 5], subcutaneous haematoma [n = 2], hypersensitivity [n = 2], drug hypersensitivity, anti factor VIII antibody positive, central venous catheterisation, staphylococcal infection, catheter site swelling, catheter management, device connection issue, haemorrhage intracranial, nausea, photophobia, headache, CSF red blood cell count positive, and gastroenteritis [n = 1 each]), and a causal relationship to damoctocog alfa pegol could not be ruled out for a total of 9 events (drug specific antibody present [n = 5], hypersensitivity [n = 2], drug hypersensitivity [n =1], anti factor VIII antibody positive [n =1]). The outcomes of these events were all reported as resolved. Seven subjects experienced 12 adverse events leading to treatment discontinuation (drug specific antibody present [n = 5], hypersensitivity [n = 2], drug hypersensitivity, anti factor VIII antibody positive, contusion, spontaneous haematoma, and spontaneous haemorrhage [n = 1 each]), and a causal relationship to damoctocog alfa pegol could not be ruled out for all those events. No deaths were reported during the study period.

7.R Outline of the review conducted by PMDA

7.R.1 Review strategy

7.R.1.1 Efficacy and safety evaluation

Since the epidemiological profile of patients with FVIII deficiency including patients with hemophilia A, the condition of bleeding tendency, the concept of FVIII replacement therapy for on-demand treatment and prophylaxis, etc., are similar between Japan and overseas, the impact of intrinsic and extrinsic ethnic factors on the efficacy and safety of damoctocog alfa pegol is not considered significant. Thus, the efficacy of prophylactic treatment with damoctocog alfa pegol in controlling bleeding tendency and the hemostatic efficacy of damoctocog alfa pegol when used on-demand and when used for surgical procedures was decided to be evaluated based on a global study, Study 13024, as the pivotal study, and Study 15912 in children aged <12 years. The safety of damoctocog alfa pegol was decided to be evaluated based on the occurrence of adverse events, inhibitor development, etc. in the main studies and extension phases of Study 13024 and Study 15912.

7.R.2 Efficacy

7.R.2.1 Efficacy of on-demand treatment

In Study 13024 (12-65 years of age), response to treatment of bleeds was rated as "excellent" or "good" for 72.4% (508 of 702) of bleeds, and the proportion of bleeds controlled by ≤2 infusions of damoctocog alfa pegol was 90.6% (636 of 702 bleeds). In Study 15912 (<12 years), response to treatment of bleeds was rated as "excellent" or "good" for 85.7% (120 of 140) of bleeds, and the proportion of bleeds controlled by ≤2 infusions of damoctocog alfa pegol was 92.1% (129 of 140 bleeds). Damoctocog alfa pegol exhibited similar efficacy in patients aged <12 years and those aged ≥12 years.

PMDA concluded that as both clinical studies demonstrated the high hemostatic efficacy of damoctocog alfa pegol, the efficacy of on-demand treatment with damoctocog alfa pegol is expected in both adult and pediatric patients.

7.R.2.2 Efficacy when used for surgical procedures

In Study 13024, the adequacy of hemostasis during and after major surgeries performed in Part B and minor surgeries performed in Part A was assessed using a predefined 4-point rating scale. Hemostatic efficacy during and after surgeries is shown in Table 21.

Table 21. Hemostatic efficacy during and after major or minor surgeries in Study 13024 (ITT)

Rating	Major surgeries (n = 17)		Minor surgeries (n = 14)	
	Intra-operative	Post-surgical	Intra-operative	Post-surgical
Excellent or good	17	13	13	10
Moderate	0	3	0	0
Poor	0	0	0	0
Unknown	0	1	1	4

Among surgeries in which hemostasis was assessed (excluding surgeries with a rating of "unknown"), the adequacy of hemostasis was rated as "excellent" or "good" in all cases, except that post-operative hemostasis was rated as "moderate" in 3 cases (major surgeries). In 2 of the 3 cases, anti factor VIII antibody positive (inhibitor development) was reported as a serious adverse event for which a causal relationship to study drug could not be ruled out, leading to study discontinuation or switching to another FVIII product [see Section 7.R.3.1].

In Study 15912, 1 subject underwent 1 minor surgery, and the adequacy of hemostasis was assessed by the investigator as "excellent."

PMDA concluded that as FVIII replacement is essential for patients with FVIII deficiency undergoing surgery, and the clinical studies demonstrated the hemostatic efficacy of damoctocog alfa pegol, the efficacy of damoctocog alfa pegol when used for surgical procedures is expected.

7.R.2.3 Efficacy of prophylactic treatment

The applicant's explanation about the efficacy endpoint for routine prophylaxis of damoctocog alfa pegol:
The primary endpoint for Study 13024 was "the responder rate." Responders were defined as subjects with "an ABR of <9 bleeds/year." An ABR of <9 bleeds/year was chosen based on the maximum ABR in patients on prophylactic treatment, predicted from the data from clinical studies with Kogenate FS or other FVIII products, etc., available at the time of designing the study. In a clinical study with thrice-weekly Kogenate FS, 72.1% of subjects demonstrated an ABR of <9 bleeds/year (*Thromb Haemost*. 2012; 108: 913-22). In a foreign post-marketing surveillance study with Refacto (an FVIII product unapproved in Japan), patients on the prophylactic treatment experienced a median ABR of 4.4 bleeds/year, and approximately 75% of subjects had an ABR of <9 bleeds/year (*Haemophilia*. 2007; 13: 131-43), etc. Thus, the endpoint of responder rate (responders defined as subjects with an ABR of <9 bleeds/year) is considered clinically meaningful. Although the ABR is a clinically important endpoint, it is expected to vary substantially according to patient characteristics, and the responder rate is less sensitive to outliers.

PMDA's view:
The objectives of routine prophylaxis are to reduce the frequency of bleeding episodes and prevent hemophilic

arthropathy (*Jpn J Thromb Hemost*. 2013; 24: 619-39). Routine prophylaxis is now widespread, and patients who achieved the goal of 0 bleeds (an ABR of 0 bleeds/year) have also been reported in a long-term observational study (*Haemophilia*. 2017; 23: 105-14, *Thromb Res*. 2017; 151: 17-22). Although responders were defined as subjects with an ABR of <9 bleeds/year in Study 13024, an ABR of <9 bleeds/year is not the best criterion in evaluating the efficacy of prophylactic treatment. On the other hand, given that the information on the ABR in patients on prophylactic treatment was limited at the time of initiating Study 13024 (in 2012), establishing the criterion based on the information on Kogenate FS etc. was unavoidable.

In Study 13024, the responder rate was higher in the prophylaxis group than in the on-demand group (Table 13), and the ABR in the prophylaxis group (median [range], 2.82 [0.0, 23.4]) was comparable to those reported with existing FVIII products (median, 1.0-3.7 bleeds/year, *Blood*. 2014;123: 317-25, *Haemophilia*. 2016; 22: 706-12, etc.) (Table 14). In Study 13024, the ABR was low, regardless of dosing frequency (twice weekly, every 5 days, every 7 days) (Table 15). Also in Study 15912, the ABR (median [range], 2.87 [0.0, 74.6]) was low. Thus, the efficacy of prophylactic treatment with damoctocog alfa pegol is expected in both adult and pediatric patients.

7.R.2.4 Consistency of results between overall population and Japanese subgroup

The results of efficacy evaluation in the overall population and Japanese subgroup in Study 13024 are shown in Table 22.

Table 22. Results of efficacy evaluation in Japanese subgroup and overall population (ITT)

		Japanese subgroup		Overall population	
		No. of subjects		No. of subjects	
Proportion of bleeds with a rating of "excellent" or "good"		11	38.0% (19/50 bleeds)	132	72.4% (508/702 bleeds)
Proportion of bleeds controlled by ≤2 infusions		11	68.0% (34/50 bleeds)	132	90.6% (636/702 bleeds)
Median ABR [range] in Weeks 0-36	Prophylaxis	10	2.85 [0.0, 7.4]	112	2.82 [0.0, 23.4]
	On-demand	1	37.27	20	23.42 [7.3, 83.2]

PMDA's view on the consistency of efficacy between the overall population and Japanese subgroup:

Although the number of Japanese subjects enrolled in Study 13024 was very limited, the ABR in the prophylaxis group was similar between the overall population and Japanese subgroup. On the other hand, the proportion of bleeds with a rating of "excellent" or "good" and the proportion of bleeds controlled by ≤2 infusions tended to be lower in the Japanese subgroup than in the overall population. These results are considered attributable to the fact that among 11 Japanese subjects, 1 subject in the on-demand group experienced 25 bleeds, and the proportion of bleeds with a rating of "excellent" or "good" and the proportion of bleeds controlled by ≤2 infusions were low in this subject (4.0% [1 of 25 bleeds] and 48.0% [12 of 25 bleeds], respectively). As this subject had 8 target joints and had experienced 64 bleeds (including 62 joint bleeds), while on on-demand treatment, in the 12 months before study entry, the subject may have had the characteristics of an easy-to-bleed state and difficulty in hemostasis. This subject had an ABR of 37.27, and there was no trend towards an increased number of bleeds after start of treatment with damoctocog alfa pegol compared with the preceding 12 months.

Taking also into account that the impact of intrinsic and extrinsic ethnic factors on the efficacy of damoctocog alfa pegol is not considered significant [see Section 7.R.1], and that a clinical pharmacology study of damoctocog alfa pegol showed no trend towards pharmacokinetic differences between the overall population and Japanese subgroup [see Section 6.2], PMDA concluded that the efficacy of damoctocog alfa pegol is expected also in Japanese patients.

7.R.3 Safety

One subject had 1 serious adverse event in Study 13401, 13 subjects had 16 serious adverse events in Part A of Study 13024 and 2 subjects had 3 serious adverse events in Part B of Study 13024, and 11 subjects had 22 serious adverse events in Study 15912. Although a causal relationship to damoctocog alfa pegol could not be ruled out for 2 events (drug hypersensitivity, overdose) in Part A of Study 13024, 3 events (anti factor VIII antibody positive [n = 2], haematoma [n =1]) in Part B of Study 13024, and 9 events (drug specific antibody present [n = 5], hypersensitivity [n = 2], drug hypersensitivity [n = 1], anti factor VIII antibody positive [n = 1]) in Study 15912, the outcome was reported as resolved for all those events, except for anti factor VIII antibody positive (n = 1) in Part B of Study 13024 (unresolved). Two subjects had 2 adverse events leading to treatment discontinuation (hypersensitivity, drug hypersensitivity) in Part A of Study 13024, 1 subject had 2 adverse events leading to treatment discontinuation (anti factor VIII antibody positive, haematoma) in Part B of Study 13024, and 7 subjects had 12 adverse events leading to treatment discontinuation (drug specific antibody present [n = 5], hypersensitivity [n = 2], drug hypersensitivity, anti factor VIII antibody positive, contusion, spontaneous haematoma, and spontaneous haemorrhage [n = 1 each]) in Study 15912. Twelve additional children aged <6 years were enrolled in Part 2 of Study 15912 and received 25 to 60 IU/kg damoctocog alfa pegol twice weekly for 12 weeks. Of whom, 2 subjects experienced 2 serious adverse events (hypersensitivity, drug ineffective), and their causal relationship to damoctocog alfa pegol could not be ruled out. Four subjects experienced 4 adverse events leading to treatment discontinuation (drug ineffective [n = 3], hypersensitivity [n = 1]).

The cases of anti factor VIII antibody positive (inhibitor development) and the formation of antibodies against damoctocog alfa pegol other than inhibitors (anti-PEG antibodies) observed in clinical studies of damoctocog alfa pegol were examined as follows.

7.R.3.1 Inhibitor development

The applicant's explanation about inhibitor development observed in clinical studies of damoctocog alfa pegol:
In clinical studies of damoctocog alfa pegol (Study 13401, Study 13024, Study 15912), 2 subjects developed an inhibitor. These cases of inhibitor development were reported as serious adverse events for which a causal relationship to damoctocog alfa pegol could not be ruled out (MedDRA/J Preferred term, anti factor VIII antibody positive) in Part B of Study 13024. These 2 subjects (Case 1, Case 2) were both enrolled in Part B for perioperative management of major surgeries, and had never received damoctocog alfa pegol. The clinical courses of these subjects are described below.

- Case 1: The subject had reduced *in vivo* recovery and a shortened elimination half-life of FVIII before study entry, and a low-titer inhibitor (0.5 Bethesda Units [BU]/mL) was detected during screening.

Although an inhibitor titer of 0.5 BU/mL was confirmed by testing before the first dose of damoctocog alfa pegol as well, as the exclusion criterion for the study (a titer ≥0.6 BU/mL) was not met, the subject received damoctocog alfa pegol and underwent scheduled surgery, and intra-operative hemostasis was rated as "good." Haematoma (reported as a serious adverse event) developed in the left thigh after surgery, and the subject received damoctocog alfa pegol and had another surgery to evacuate the haematoma. The adequacy of hemostasis during the second surgery was rated as "good" while the adequacy of hemostasis after the second surgery was rated as "moderate." After the second surgery, the subject switched to another FVIII product that the subject had previously used before study participation, for better hemostatic control. A low-titer inhibitor (0.6 BU/mL and 0.7 BU/mL) was detected in blood samples collected immediately before the first surgery and after the second surgery. This subject received a total of 29 infusions of damoctocog alfa pegol during and after the first surgery, and 7 weeks after switching to another FVIII product, the inhibitor titer rose to 2.7 BU/mL, but the subject's condition was reported to be good.

- Case 2: The subject had a history of inhibitor. A shortened elimination half-life and mild flushing (hypersensitivity) were reported after 1 dose of damoctocog alfa pegol for pre-surgical pharmacokinetic evaluation. Although the inhibitor titer was 1.7 BU/mL, the subject used steroids and antihistamines concomitantly and underwent surgery. While intra-operative hemostasis was rated as "good," post-operative hemostasis was rated as "moderate," and the subject switched to another FVIII product that the subject had previously used before study participation. No inhibitors were detected by testing at 2 weeks after surgery. The subject's condition was also reported to be good after switching to another FVIII product.

Case 1: The subject was considered having a pre-existing low-titer inhibitor before study entry.
Case 2: The positive inhibitor result was considered transient.

In Study 15912, inhibitor formation did not occur. Although 1 case of anti factor VIII antibody positive was reported as a serious adverse event for which a causal relationship to damoctocog alfa pegol could not be ruled out, the subject tested negative for inhibitors at 5 days, 3 weeks, and 9 weeks after the occurrence of this event.

PMDA's view:
Two subjects who developed an inhibitor in Part B of Study 13024 had a pre-treatment low-titer inhibitor or a history of inhibitor, and it is difficult to draw a conclusion on the risk of inhibitor development associated with damoctocog alfa pegol, based on the results of clinical studies. However, since, as with existing FVIII products, neutralization by inhibitors may affect the efficacy of damoctocog alfa pegol, information on inhibitor development is very important. Thus, it is necessary to provide post-marketing information to healthcare professionals in clinical practice appropriately and promptly.

7.R.3.2 Formation of anti-PEG antibodies

In clinical studies of damoctocog alfa pegol, the formation of anti-PEG antibodies (antibodies that recognize the PEG moiety of damoctocog alfa pegol [different from inhibitors, i.e. neutralizing antibodies to FVIII])

occurred. The applicant's explanation about the relationship between the formation of anti-PEG antibodies and loss of efficacy (including not only adverse events of "drug ineffective" reported but also those detected clinically by the occurrence of bleeding events, decreased FVIII activity, etc.)/hypersensitivity reactions observed in clinical studies:

Loss of efficacy was observed in 7 of 61 subjects in the main study of Study 15912 and 4 of 12 subjects in Part 2 of Study 15912. Table 23 shows the occurrence of loss of efficacy and hypersensitivity reactions and the occurrence of those events possibly related to anti-PEG antibodies by age group. In Study 13401 and Study 13024, which did not provide a definition of adverse events of special interest for "loss of efficacy," serious breakthrough bleeds were assessed retrospectively for potential involvement of loss of efficacy, but there were no serious breakthrough bleeds which were considered attributable to loss of efficacy. All of the subjects with loss of efficacy were <6 years. Many of the subjects developed anti-PEG antibodies within the first 4 exposure days, resulting in reduced *in vivo* recovery or FVIII activity after the infusion of damoctocog alfa pegol, and loss of efficacy.

Table 23. Occurrence of loss of efficacy/hypersensitivity reactions leading to study discontinuation by age group (Safety analysis population)

	Study 15912 (Main study and Part 2)		Study 13024 (Main study and extension)
	<6 years (N = 44)	≥6 and <12 years (N = 29)	≥12 years (N = 134)
No. of subjects with loss of efficacy	11 [a]	0	0
No. of subjects with loss of efficacy possibly related to anti-PEG antibodies	10/11 [b]	-	-
No. of subjects with hypersensitivity reaction	3	1	2
No. of subjects with hypersensitivity reaction possibly related to anti-PEG antibodies	3/3	0/1	1/2

a: Including 3 subjects who also had hypersensitivity reactions.
b: Including 1 subject in whom anti-PEG antibody was not detected, but neutralizing antibody to damoctocog alfa pegol was detected.

The relationship between the presence or absence of anti-PEG antibodies at baseline and loss of efficacy of damoctocog alfa pegol/hypersensitivity reactions was assessed. The proportion of subjects with positive baseline anti-PEG antibodies was the highest in children aged <6 years and decreased with increasing age (Table 24). There were subjects with positive baseline anti-PEG antibodies who did not develop clinical symptoms, and pre-existing anti-PEG antibodies were not predictive of loss of efficacy or hypersensitivity reactions.

Table 24. Subjects with positive baseline anti-PEG antibodies (Safety analysis population)

	Study 15912 (Main study and Part 2)		Study 13024 (Main study and extension)
	<6 years (N = 44)	≥6 and <12 years (N = 29)	≥12 years (N = 134)
No. of subjects with positive baseline anti-PEG antibodies [a]	12/44 (27.3%)	3/29 (10.3%)	3/114 (2.6%)
No. of those subjects with clinical symptoms due to an immune response to PEG	6/12	0/3	1/3

a: Subjects who tested positive for anti-PEG antibodies by an assay that has the highest sensitivity for IgG detection and can also detect IgM, IgE, and IgA antibodies, or an assay with high sensitivity for IgM detection

Based on the above, loss of efficacy possibly related to anti-PEG antibodies occurred more frequently in patients aged <6 years than in patients aged ≥6 years, and the favorable risk-benefit profile of damoctocog alfa pegol could not be established. Although the safety profile in patients aged ≥6 and <12 years was similar to

that in patients aged ≥12 years, the age at which the risk of an immune response to PEG is sufficiently reduced or eliminated is undefined. Thus, damoctocog alfa pegol should not be indicated for use in children aged <12 years.

In Study 13401 and Study 13024 in patients aged ≥12 years, among 148 subjects treated with damoctocog alfa pegol, 8 subjects tested positive for anti-PEG antibodies at any time point during the study period. Of whom, only 1 subject developed a hypersensitivity reaction possibly related to anti-PEG antibodies. As many of the subjects with loss of efficacy in the clinical study developed anti-PEG antibodies within the first 4 exposure days, it is important to carefully monitor patients in the early phase of treatment. Note that hypersensitivity reactions possibly related to anti-PEG antibodies were easily diagnosed, short in duration, and resolved following discontinuation of treatment. Based on the above, post-marketing monitoring for anti-PEG antibodies is not mandatory.

Although loss of efficacy is unlikely to occur in patients aged ≥12 years, the package insert etc. will advise that the following procedures should be followed if the expected hemostatic effects are not achieved during treatment with damoctocog alfa pegol (if increased bleeding or bruising, reduced hemostatic effects, lower *in vivo* recovery after the infusion of damoctocog alfa pegol, etc. are observed).

(1) Suspect the development of inhibitors or anti-PEG antibodies. Determine *in vivo* recovery after the infusion of damoctocog alfa pegol and conduct testing for inhibitors.
(2) In the case of reduced *in vivo* recovery and a positive inhibitor result, make a definitive diagnosis of FVIII inhibitor, and treat patients in accordance with the hemostatic treatment guidelines for congenital hemophilia patients who possess inhibitors.
(3) In the case of reduced *in vivo* recovery and a negative inhibitor result, the development of anti-PEG antibodies is suspected. As anti-PEG antibodies do not cross-react with unmodified FVIII products, discontinue treatment with damoctocog alfa pegol and switch patients to a previously effective FVIII product. In a clinical study of damoctocog alfa pegol, there were no problems concerning *in vivo* recovery or efficacy after switching to another FVIII product that the subject had previously used before study participation.

PMDA's view:

The applicant's conclusion (damoctocog alfa pegol should not be indicated for use in patients aged <12 years, considering the risk of loss of efficacy observed in Study 15912 in patients aged <12 years) is acceptable. In Study 13401 and Study 13024 in patients aged ≥12 years, loss of efficacy was not observed. However, since the number of patients assessed in the clinical studies was limited, and 1 case of hypersensitivity reaction possibly related to anti-PEG antibodies has been reported also among patients aged ≥12 years, it is necessary to provide information on adverse events possibly related to anti-PEG antibodies and their management via package insert etc. Information on loss of efficacy and hypersensitivity reactions should continue to be collected via post-marketing surveillance etc.

7.R.4 Indication

The applicant's explanation about the indication for damoctocog alfa pegol:

Study 13024 in patients with severe hemophilia A aged ≥12 years demonstrated the efficacy of damoctocog alfa pegol for on-demand treatment, perioperative management, and routine prophylaxis and its favorable safety profile. Based on the above, the proposed indication for damoctocog alfa pegol is "control of bleeding tendency in patients with blood coagulation factor VIII deficiency." Given the occurrence of adverse events possibly related to anti-PEG antibodies in Study 15912 in patients with severe hemophilia A aged <12 years, the favorable risk-benefit profile of damoctocog alfa pegol could not be established. Thus, damoctocog alfa pegol should not be indicated for use in children aged <12 years [see Section 7.R.3].

PMDA's view:

The applicant's explanation is acceptable. For patients aged ≥12 years, the clinical positioning of damoctocog alfa pegol should be the same as that of existing FVIII products.

7.R.5 Dosage and administration

7.R.5.1 Dosing regimen for on-demand treatment

The applicant's explanation about the dosing regimen for on-demand treatment:

In Study 13024 in patients with severe hemophilia A aged ≥12 years, the dose and the dosing frequency for multiple doses for the treatment of bleeding were determined by the investigator, according to the type, severity, and location of the bleeding event, based on each subject's prior experience with treatment of bleeding events, WFH's guidelines, etc. The median dose per infusion for the treatment of bleeding [range] was 31.7 [14, 62] IU/kg in the main study of Study 13024.

Taking account of dosing of damoctocog alfa pegol in the clinical study as described above, the need to determine the dosage required to treat bleeding events according to the type, severity, and location of the bleeding event, and the dosage and administration statements for currently approved recombinant FVIII products, the proposed dosage and administration statement for on-demand treatment is "the usual dose is 10 to 30 IU/kg body weight. This may be adjusted according to the patient's condition." A guide for dosing damoctocog alfa pegol (dose and frequency) for on-demand treatment and perioperative management will be provided in the precautions for dosage and administration section of the package insert.

PMDA considers that the applicant's explanation is acceptable.

7.R.5.2 Dosing regimen for routine prophylaxis

The applicant's explanation about the dosing regimen for routine prophylaxis:

In Study 13024, in order to identify high bleeders who did not qualify for randomization to a less frequent dosing regimen, subjects started treatment with twice weekly infusions of a low dose (25 IU/kg) of damoctocog alfa pegol during the 10-week run-in phase and subsequently received 30 to 40 IU/kg twice weekly, 45 to 60 IU/kg every 5 days, or 60 IU/kg every 7 days. As a result, similar results were obtained, regardless of dosing frequency. Subjects who experienced a marked increase in bleeding frequency were allowed to increase their

dose with the same dosing frequency or switch to more frequent dosing regimens. While 16.3% (7 of 43) of subjects in the every 5-day treatment group increased their dose and 25.6% (11 of 43) of subjects in the every 7-day treatment group changed their dosing frequency, most subjects remained on the assigned regimen.

None of the subjects in the every 5-day treatment group changed their dosing frequency, and this dosing regimen was considered to produce stable effects. Thus, the proposed dosage and administration statement is "the usual regimen for routine prophylaxis is 45 to 60 IU/kg body weight every 5 days. The dose and frequency may be adjusted to 60 IU/kg body weight once weekly or 30 to 40 IU/kg body weight twice weekly, according to the patient's condition."

PMDA's view:
In Study 13024, subjects' dosing regimens were selected, according to their bleeding frequency during the 10-week run-in phase in which subjects received the twice-weekly regimen, and the efficacy and safety of prophylactic treatment was demonstrated. Thus, taking account of the study design and dosing schedule for the clinical study, the appropriate dosage and administration statement should be "the usual regimen is 30 to 40 IU/kg body weight twice weekly. The regimen may be adjusted to 45 to 60 IU/kg body weight every 5 days or 60 IU/kg body weight once weekly, according to the patient's condition." Since the dosing regimen during the run-in phase of Study 13024 (25 IU/kg twice weekly) was intended to identify high bleeders by administering low-dose damoctocog alfa pegol, it is not necessary to include this regimen in the dosage and administration section of the package insert. However, the package insert should advise that for routine prophylaxis, an appropriate dosing regimen should be selected, considering the patient's condition such as their most recent bleeding experience.

The dosage and administration section of the package insert should reflect the above considerations in Section 7.R.5.1 and Section 7.R.5.2, and specify that damoctocog alfa pegol is indicated in patients aged ≥12 years, as shown below.

Dosage and Administration
The product should be reconstituted with the total volume of diluent supplied and infused by slow intravenous injection at a rate not exceeding 2.5 mL/min.

For adults and children aged ≥12 years, the usual dose is 10 to 30 IU/kg body weight. This may be adjusted according to the patient's condition.

For adults and children aged ≥12 years, the usual regimen for routine prophylaxis is 30 to 40 IU/kg body weight twice weekly. The regimen may be adjusted to 45 to 60 IU/kg body weight every 5 days or 60 IU/kg body weight once weekly, according to the patient's condition.

Precautions for Dosage and Administration (the statement regarding routine prophylaxis only)
For routine prophylaxis, an appropriate dosing regimen should be selected, considering the patient's condition

such as their most recent bleeding experience (see “Clinical Studies”).

7.R.6 Post-marketing investigations

The applicant's explanation about post-marketing surveillance of damoctocog alfa pegol:

The applicant is planning to conduct a drug use-results survey in patients with FVIII deficiency aged ≥12 years, previously treated with FVIII products (target sample size, 60 patients; observation period, 2 years) to assess the safety and efficacy of damoctocog alfa pegol in clinical practice. The target sample size was determined based on patient exposure estimated from market research etc. in Japan, taking account of feasibility. The planned survey period is 5 years and 6 months. Inhibitor development and the occurrence of adverse events including shock and anaphylaxis will be investigated in this survey.

PMDA's view:

Since the number of Japanese subjects included in clinical studies of damoctocog alfa pegol was very limited, and there is little clinical experience with damoctocog alfa pegol under the Japanese medical environment, it is necessary to conduct post-marketing surveillance in clinical practice. In clinical studies of damoctocog alfa pegol, loss of efficacy was associated with the development of anti-PEG antibodies in patients aged <6 years, and there was also a subject aged ≥6 years who tested positive for anti-PEG antibodies after the first infusion of damoctocog alfa pegol. Given these findings, it is necessary to continue to watch for the occurrence of loss of efficacy and hypersensitivity reactions possibly related to anti-PEG antibodies. It is important to evaluate safety information obtained from post-marketing surveillance, compared with safety information from clinical studies submitted, and determine the need for further information.

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

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

The inspection and assessment are currently ongoing, and their results and PMDA's conclusion will be reported in the Review Report (2).

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

The inspection is currently ongoing, and its results and PMDA's conclusion will be reported in the Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that damoctocog alfa pegol has efficacy in controlling bleeding tendency in patients with blood coagulation factor VIII deficiency, and that damoctocog alfa pegol has acceptable safety in view of its benefits. Damoctocog alfa pegol is clinically meaningful because it offers a new treatment option for the control of bleeding tendency in patients with blood coagulation factor VIII deficiency.

PMDA has concluded that damoctocog alfa pegol may be approved if damoctocog alfa pegol is not considered to have any particular problems based on further discussion on its efficacy and safety, post-marketing surveillance, etc., at the Expert Discussion.

Review Report (2)

July 31, 2018

Product Submitted for Approval

Brand Name	Jivi for IV Injection 250, Jivi for IV Injection 500, Jivi for IV injection 1000, Jivi for IV Injection 2000, Jivi for IV Injection 3000
Non-proprietary Name	Damoctocog Alfa Pegol (Genetical Recombination)
Applicant	Bayer Yakuhin, Ltd.
Date of Application	October 17, 2017

List of Abbreviations

See Appendix.

1. Content of the Review

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

At the Expert Discussion, the expert advisors supported PMDA's conclusions on issues presented in the Review Report (1) (Section "7.R.2 Efficacy," Section "7.R.3 Safety," Section "7.R.4 Indication").

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

1.1 Dosage and administration

The expert advisors supported PMDA's conclusion presented in Section "7.R.5 Dosage and administration" in the Review Report (1), and made the following comment.

- Since plasma FVIII level at ≥1% cannot be maintained in all subjects treated prophylactically with 60 IU/kg every 5 or 7 days [see Review Report (1) Section 6.2.1.4], the twice weekly regimen should be recommended with the option of the every 5- or 7-day regimen. For prophylactic treatment with damoctocog alfa pegol, it is important to determine trough plasma FVIII levels.

PMDA instructed the applicant to modify the proposed dosage and administration statement as shown below.

Dosage and Administration

The product should be reconstituted with the total volume of diluent supplied and infused by slow intravenous injection at a rate not exceeding 2.5 mL/min.

For patients aged ≥12 years, the usual dose is 10 to 30 IU/kg body weight. This may be adjusted according to the patient's condition.

For patients aged ≥12 years, the usual regimen for routine prophylaxis is 30 to 40 IU/kg body weight twice weekly. The regimen may be adjusted to 45 to 60 IU/kg body weight every 5 days or 60 IU/kg body weight once weekly, according to the patient's condition.

1.2 Risk management plan (draft)

The expert advisors supported PMDA's conclusion presented in Section "7.R.6 Post-marketing investigations" in the Review Report (1), and made the following comments.

- Detailed information on inhibitor development observed in clinical studies of damoctocog alfa pegol (surgery type, the dose and dose interval of damoctocog alfa pegol, subject's course, etc.) should be provided to healthcare professionals in clinical practice as appropriate. It is also necessary to collect post-marketing information on inhibitor development.
- Since damoctocog alfa pegol is a PEGylated protein, and loss of efficacy/hypersensitivity reactions possibly related to anti-PEG antibodies were observed in clinical studies, it is important to collect post-marketing information on anti-PEG antibody formation and investigate its safety. The possibility of PEG accumulation in the body should also be noted.

In view of the above comments from the expert advisors, PMDA has concluded that the risk management plan (draft) for damoctocog alfa pegol should include the safety specification presented in Table 25, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 26 and Table 27. The applicant agreed to take appropriate action concerning the risk management plan (draft).

Table 25. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
· Inhibitor development · Anti-PEG antibody formation	· Shock, anaphylaxis · Dose errors associated with FVIII activity assays	None
Efficacy specification		
None		

Table 26. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
· Early post-marketing phase vigilance · Use-results survey	· Early post-marketing phase vigilance · Organize and disseminate informative materials to healthcare professionals

Table 27. Outline of use-results survey (draft)

Objective	To assess the safety and efficacy of damoctocog alfa pegol in clinical practice (including long-term use).
Survey method	Central registry system
Population	Previously treated patients with FVIII deficiency aged ≥12 years
Observation period	2 years
Planned sample size	60 patients
Main survey items	Patient characteristics, the use of damoctocog alfa pegol (prophylactic treatment, on-demand treatment, perioperative management), concomitant medications/therapies, clinical laboratory tests (measurement of FVIII activity, inhibitor measurement, pharmacokinetic assessment, etc.), adverse events, efficacy

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

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

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

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

The new drug application data (CTD 5.3.5.2.1, CTD 5.3.5.2.3, CTD 5.3.5.2.5) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

3. Overall Evaluation

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

Indication

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

Dosage and Administration

The product should be reconstituted with the total volume of diluent supplied and infused by slow intravenous injection at a rate not exceeding 2.5 mL/min.

For patients aged ≥12 years, the usual dose is 10 to 30 IU/kg body weight. This may be adjusted according to the patient's condition.

For patients aged ≥12 years, the usual regimen for routine prophylaxis is 30 to 40 IU/kg body weight twice weekly. The regimen may be adjusted to 45 to 60 IU/kg body weight every 5 days or 60 IU/kg body weight once weekly, according to the patient's condition.

Condition of Approval

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

Appendix

List of Abbreviations

ABR	Annualized number of bleeds
APC	Activated protein C
aPTT	Activated partial thromboplastin time
AUC	Area under the curve
BDD-rFVIII	B domain deleted-recombinant human coagulation factor VIII
BHK-21 cell	Baby Hamster Kidney 21 Cell
BMI	Body mass index
BU	Bethesda unit
CAL	Cells at the limit of *in vitro* cell age used for production
CL	Clearance
C_{max}	Maximum plasma concentration
CQA	Critical quality attribute
CSF	Cerebrospinal fluid
damoctocog alfa pegol	Damoctocog Alfa Pegol (Genetical Recombination)
ELISA	Enzyme-linked immunosorbent assay
[redacted]	[redacted]
FIXa	Activated coagulation factor IX
FVIII	Coagulation factor VIII
FVIII KO mice	FVIII-deficient mice
FX	Coagulation factor X
FXa	Activated coagulation factor X
HCP	Host cell protein
HPLC	High performance liquid chromatography
ICH	International council for harmonisation of technical requirements for pharmaceuticals for human use
IgG	Immunoglobulin G
Inhibitors	Neutralizing antibodies against FVIII
ITT	Intent-to-treat
IU	International units
Kogenate FS	Kogenate FS BIO-SET for injection
MCB	Master cell bank
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MMV	Mouse minute virus
[redacted]	[redacted]
MRT	Mean residence time
NZW	New Zealand White
PEG	Polyethylene glycol
PEG-60-Mal-Cys	Approximately 60 kDa PEG-maleimide linker-cysteine
PMDA	Pharmaceuticals and Medical Devices Agency
PPV	Porcine parvovirus
PRV	Pseudorabies virus
QbD	Quality by design
Reo 3	Reovirus type 3
rFVIII	Recombinant FVIII
[redacted]	[redacted]
$t_{1/2}$	Elimination half-life
[redacted]	[redacted]
TEG	thromboelastography
SD	Sprague Dawley

SDS-PAGE	Sodium dodecyl sulfate-polyacrylamide gel electrophoresis
[redacted]	[redacted]
[redacted]	[redacted]
V_c	Volume of distribution central compartment
V_{ss}	Volume of distribution at steady-state
vWF	von Willebrand Factor
WBCT	whole blood clotting time
WCB	Working cell bank
WFH	World Federation of Hemophilia
X-MuLV	Xenotropic murine leukemia virus