Report on the Deliberation Results

September 12, 2017
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour, and Welfare

Brand Name	Afstyla I.V. Injection 250
	Afstyla I.V. Injection 500
	Afstyla I.V. Injection 1000
	Afstyla I.V. Injection 1500
	Afstyla I.V. Injection 2000
	Afstyla I.V. Injection 2500
	Afstyla I.V. Injection 3000
Non-proprietary Name	Lonoctocog Alfa (Genetical Recombination) (JAN*)
Applicant	CSL Behring K.K.
Date of Application	October 27, 2016

Results of Deliberation

In its meeting held on September 8, 2017, 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

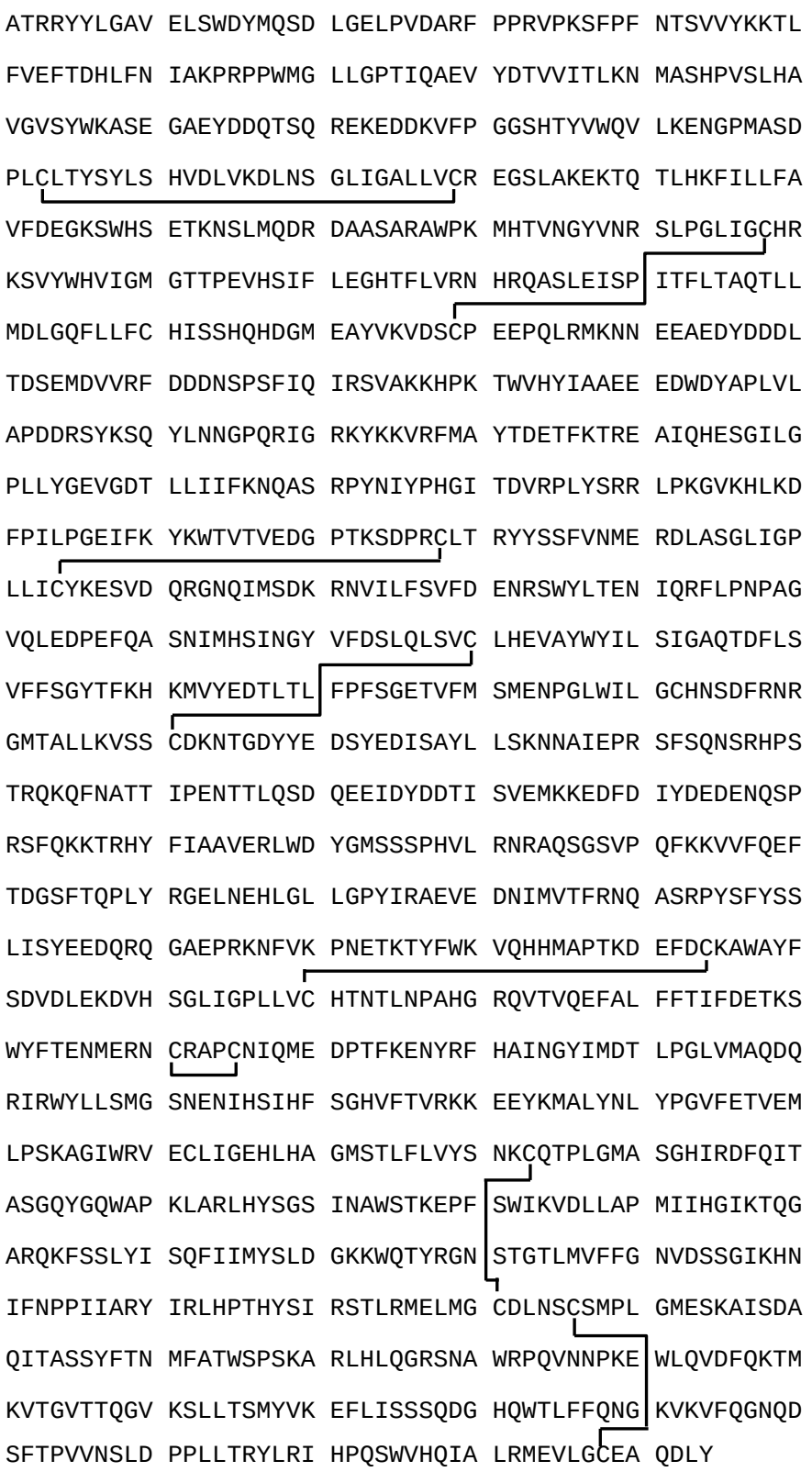
August 21, 2017
Pharmaceuticals and Medical Devices Agency

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	Afstyla I.V. Injection 250 Afstyla I.V. Injection 500 Afstyla I.V. Injection 1000 Afstyla I.V. Injection 1500 Afstyla I.V. Injection 2000 Afstyla I.V. Injection 2500 Afstyla I.V. Injection 3000
Non-proprietary Name	Lonoctocog Alfa (Genetical Recombination)
Applicant	CSL Behring K.K.
Date of Application	October 27, 2016
Dosage Form/Strength	Solution for injection. Each vial contains 250, 500, 1000, 1500, 2000, 2500, or 3000 International Units (IU) of Lonoctocog Alfa (Genetical Recombination) requiring reconstitution before use.
Application Classification	Prescription drug, (1) Drugs with a new active ingredient
Definition	Lonoctocog Alfa is a recombinant human blood coagulation factor VIII analog corresponding to amino acids 1 to 764 and 1653 to 2332 of human blood coagulation factor VIII. Lonoctocog Alfa is produced in Chinese hamster ovary cells. Lonoctocog Alfa is a glycoprotein (molecular weight: approximately 170,000) consisting of 1444 amino acid residues.

Structure

Amino acid sequence and disulfide bonds:

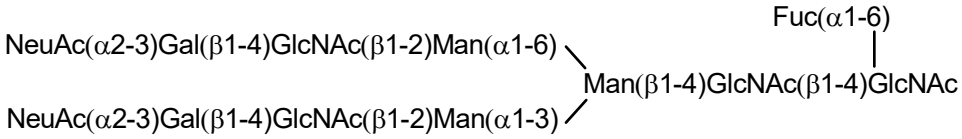


Y346, Y718, Y719, Y723, Y776, Y792: sulfation; N41, N239, N757, N764, N922, N1230: glycosylation; S741, S743, S746, T759, T760, T765, T766, S769, S781: potential glycosylation sites

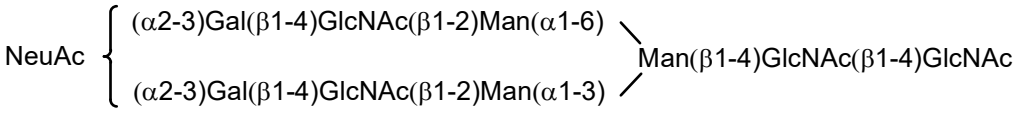
Estimated main glycan structures:

N-linked glycans

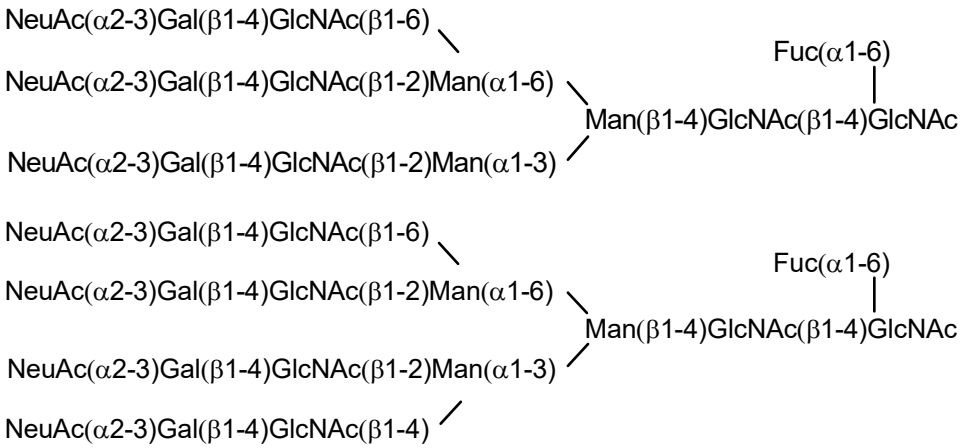
N41



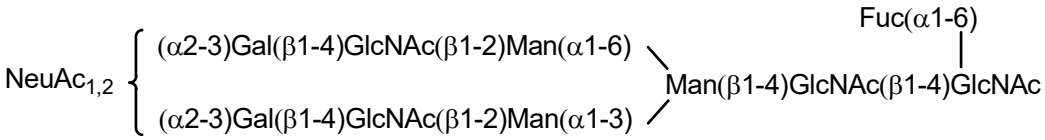
N239



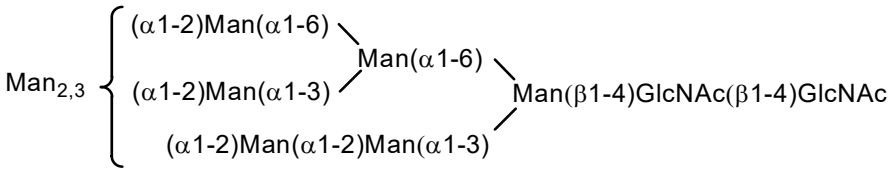
N757, N764



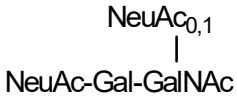
N922



N1230



O-linked glycans



Molecular formula: $C_{7470}H_{11355}N_{1991}O_{2196}S_{68}$ (protein portion)
Molecular weight: Approximately 170,000

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 routine clinical practice should be further evaluated in post-marketing surveillance.

Indication

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

Dosage and Administration

The product is reconstituted with the entire vial of the solvent supplied and is slowly injected intravenously.
The usual dosage is 10 to 30 International Units (IU) per kg (body weight). The dose may be adjusted according to the patient's condition.
The usual dosage for routine prophylaxis is 20 to 50 IU per kg (body weight) administered 2 or 3 times weekly.

Condition of Approval

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

Attachment

Review Report (1)

June 14, 2017

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

Product Submitted for Approval

Brand Name	Afstyla I.V. Injection 250 Afstyla I.V. Injection 500 Afstyla I.V. Injection 1000 Afstyla I.V. Injection 1500 Afstyla I.V. Injection 2000 Afstyla I.V. Injection 2500 Afstyla I.V. Injection 3000
Non-proprietary Name	Lonoctocog Alfa (Genetical Recombination)
Applicant	CSL Behring K.K.
Date of Application	October 27, 2016
Dosage Form/Strength	Solution for injection. Each vial contains 250, 500, 1000, 1500, 2000, 2500, or 3000 International Units (IU) of Lonoctocog Alfa (Genetical Recombination) requiring reconstitution before use.
Proposed Indication	Control of bleeding tendency in patients with blood coagulation factor VIII deficiency

Proposed Dosage and Administration

The product is reconstituted with the entire vial of the solvent supplied and is slowly injected intravenously.

The dose for on-demand treatment of bleeding is calculated based on the patient's body weight and the required blood coagulation factor VIII activity level in circulating plasma.

The usual starting dose for routine prophylaxis is 20 to 50 IU per kg (body weight) administered 2 or 3 times weekly. The dosage regimen may be adjusted according to the patient's condition.

Table of Contents

List of Abbreviations

[redacted]	[redacted]
[redacted]	[redacted]
Advate	Advate®
aPTT	Activated partial thromboplastin time
AsBR	Annualized spontaneous bleeding rate
AUC	Area under the curve
$AUC_{0-\infty}$	Area under the curve up to infinity
BVDV	Bovine viral diarrhea virus
CAL	Cells at the limit of *in vitro* cell age used for production
CHO	Chinese Hamster Ovarian
CI	Confidence interval
CL	Clearance
C_{max}	Maximum plasma concentration
CPV	Canine parvovirus
CQA	Critical quality attributes
EVA	Ethylene vinyl acetate
Feiba	FEIBA NF
FVIII	Blood coagulation factor VIII
FVIII KO mouse	Blood coagulation factor VIII knockout mouse
FX	Blood coagulation factor X
FXa	Activated form of blood coagulation factor X
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
Impurity 2	[redacted]
Impurity 10	[redacted]
IR	Incremental recovery

IU	International Units
Lonoctocog alfa	Lonoctocog alfa (genetical recombination)
MCB	Master cell bank
MRT	Mean retention time
MuLV	Murine leukemia virus
NZW	New Zealand White
PMDA	Pharmaceuticals and Medical Devices Agency
PRV	Pseudorabies virus
QbD	Quality by design
RCB	Research cell bank
RH	Relative Humidity
rFVIII-SC	Recombinant blood coagulation factor VIII Single Chain
SD	Sprague Dawley
SDS-PAGE	Sodium dodecyl sulfate-polyacrylamide gel electrophoresis
Study 1001	Study CSL627_1001
Study 3001	Study CSL627_3001
Study 3002	Study CSL627_3002
$t_{1/2}$	Elimination half-life
TEG	Thromboelastography
TEM	Thromboelastometry
TGA	Thrombin generation assay
V_{ss}	Volume of distribution at steady-state
vWF	von Willebrand Factor
WCB	Working cell bank
WFH	World Federation of Hemophilia

1. Origin or history of discovery, use in foreign countries, and other information

Hemophilia A (congenital blood coagulation factor VIII deficiency), a bleeding disorder that is caused by a quantitative decrease in or a qualitative abnormality of blood coagulation factor VIII (FVIII), may lead to serious bleeding episodes. The primary treatment for patients with hemophilia A is to administer an adequate dose of FVIII to ensure hemostasis. To date, several human plasma-derived FVIII products and recombinant FVIII products have been approved as FVIII products in Japan.

Lonoctocog Alfa (Genetical Recombination) (hereinafter referred to as "lonoctocog alfa") is a single-chain recombinant human FVIII analog with covalent linkage between heavy and light chains of FVIII. Upon cleavage by thrombin in the body, it is converted into an endogenous active FVIII form and exhibits blood clotting activity. Its design as a single-chain structure form of FVIII is expected to contribute to the avoidance of separation of heavy and light chains before activation and the enhancement of manufacturing efficiency.

For the development of lonoctocog alfa, a global phase I/III study (Study 1001) in patients with hemophilia A aged ≥12 and ≤65 years was initiated in [redacted] 20[redacted] in a total of 20 countries including Japan, and a foreign phase III study (Study 3002) in patients with hemophilia A aged <12 years was initiated in [redacted] 20[redacted]. Based on the results from these 2 clinical studies, the marketing application for lonoctocog alfa has been submitted. Lonoctocog alfa was approved in the US in May 2016 and in Europe in January 2017.

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

2.1 Drug substance

2.1.1 Preparation and control of cell substrate

The gene of lonoctocog alfa is a construct in which the coding sequences for most of the B-domain occurring in full-length FVIII obtained from human liver mRNA (amino acids 765-1652 of full-length FVIII) has been removed. The gene of lonoctocog alfa was inserted in an expression vector by recombinant technology, and the lonoctocog alfa gene expression construct obtained was transfected into Chinese Hamster Ovarian (CHO) cells, and a cell line highly expressing lonoctocog alfa was isolated. From this cell line, a research cell bank (RCB), master cell bank (MCB), and working cell bank (WCB) were sequentially prepared.

Characterization and purity tests were performed for the MCB, WCB, and cells at the limit of *in vitro* cell age used for production (CAL) in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q5A (R1), Q5B, and Q5D, which demonstrated the genetic stability of the cell bank system during the manufacturing of lonoctocog alfa. No viral or non-viral adventitious agents were detected other than Impurity 1, which is known to be present in rodent cell lines, within the scope of the tests performed.

Appropriate storage conditions have been established for the MCB and WCB. There is no plan for generating a new MCB or WCB at present.

2.1.2 Manufacturing process

The manufacturing process for the drug substance consists of the following steps: [redacted], and virus removal filtration. The drug substance is stored in an ethylene vinyl acetate (EVA) copolymer bag at ≤−65°C.

All the manufacturing process steps for the drug substance are defined as critical steps.

A filtrate obtained after viral inactivation by [redacted] is regarded as an intermediate of the drug substance, which is appropriately controlled in terms of its specifications, storage temperature, and storage period. Process validation of the commercial-scale manufacturing process for the drug substance was carried out.

2.1.3 Safety evaluation of adventitious agents

Except for the host CHO cell line, no animal-derived raw materials are used in the drug substance manufacturing process. The CHO cell line has been confirmed to meet the Standards for Biological Ingredients.

Purity tests were performed on the MCB, WCB, and CAL. As a result, no viral or non-viral adventitious agents were detected.

Tests for [redacted], mycoplasma, adventitious viruses (*in vitro*), and [redacted] were performed for [redacted]. As a result, no viral or non-viral adventitious agents were detected.

Viral clearance studies of the manufacturing process were performed with model viruses as shown in Table 1, which demonstrated a certain robustness of the viral clearance in the purification process. The virus reduction factors for each step shown in the table were the lowest values among the results of multiple independent viral clearance studies ([redacted]).

Table 1. Results of viral clearance studies

Manufacturing process step	Virus reduction factor (log_{10})			
	MuLV	BVDV	PRV	CPV
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Virus removal filtration	[redacted]	[redacted]	[redacted]	[redacted]
Overall virus reduction factor[a]	≥17.2 (≥13.5)	≥13.7 (≥10.3)	≥18.4 (≥13.5)	≥10.0 (≥6.9)

a Because a study for [redacted] using a reused resin was not conducted more than once under the same conditions, overall virus reduction factors without including the virus reduction factors for this step are shown in parentheses.

2.1.4 Manufacturing process development (comparability)

Major changes made to the drug substance manufacturing process during development were as shown below (pre-change and post-change manufacturing processes are defined as Process A and Process B, respectively).

- [redacted]
- [redacted]
- [redacted]
- [redacted]

The drug product used in toxicity studies, the phase I/III study, and the phase III study was manufactured using the drug substance manufactured by Process A, the drug substances manufactured by Process A or B, and the drug substance manufactured by Process B, respectively [see Sections "7.1 Phase I/III study" and "7.2 Phase III study"]. When changes were made in the manufacturing process, comparability studies on quality attributes were performed, which demonstrated comparability between pre-change and post-change drug substances.

A quality by design (QbD) approach was used for manufacturing process development [see Section "2.3 QbD"].

2.1.5 Characterization

2.1.5.1 Structure, physicochemical properties, and biological properties

The drug substance was characterized by the tests shown in Table 2.

Table 2. Summary of characterization

Item	
Structure	• Primary structure, disulfide bonds, free thiol group • Glycosylation (N- and O-linked glycans) • Amino acid modifications (tyrosine sulfation, methionine oxidation, and deamidation) • Secondary structure, high-order structure
Physicochemical properties	• Molar absorptivity • Molar specific activity and mass specific activity
Biological properties	• Thrombin formation capacity • Blood coagulation factor X (FX) activation by tenase complex formation • Changes of recombinant blood coagulation factor VIII single chain (rFVIII-SC) structure and clotting activity by activated protein C/protein S pathway, activated form of blood coagulation factor X (FXa), or thrombin • FVIII activity • Binding property to von Willebrand factor (vWF) and phospholipid endoplasmic reticulum

2.1.5.2 Product-related substances/Product-related impurities

Based on the results of characterization, active truncated forms are classified as product-related substances, and dimers, multimers and aggregates, inactive truncated forms, oxidized forms, and deamidated forms are classified as product-related impurities. Dimers, multimers and aggregates, and truncated forms are controlled by specifications for the drug substance and drug product.

2.1.5.3 Process-related impurities

Impurities 2, 3, 4, 5, 6, 7, 8, 9, 10, and 11 are considered process-related impurities. It has been confirmed that all of the process-related impurities are adequately removed through the manufacturing process.

[redacted], bacterial endotoxins, and Impurities 2, 8, and 11 are controlled by specifications for the drug substance, and bacterial endotoxins are also controlled by specifications for the drug product.

2.1.6 Control of drug substance

The proposed specifications for the drug substance consist of description, identification (sodium dodecyl sulfate-polyacrylamide gel electrophoresis [SDS-PAGE], peptide map, and [redacted]), [redacted], purity (Related Substance 1 [redacted], [redacted] [redacted], [redacted], Impurity 2 [redacted], Impurity 8, and Impurity 11), bacterial endotoxins, [redacted], potency (synthetic substrate method), and [redacted].

2.1.7 Stability of drug substance

Table 3 outlines the major stability studies of the drug substance.

Table 3. Outline of major stability studies of the drug substance

	Number of batches tested	Storage conditions	Study period	Storage container
Long-term	4	≤−65°C	36 months	EVA copolymer bag
Accelerated	3	−30°C to −15°C	9 weeks	
Stress (light)	1	25°C, 65% RH	Overall illumination: ≥1.2 million lux·h, Integrated near ultraviolet energy: ≥200 W·h/m^2	Glass vial
Stress (temperature)	1	40°C	2 weeks	

There were no significant changes in the drug substance over time under the long-term and accelerated conditions and specifications were met throughout the testing period. In the stress testing (light and temperature), the drug substance showed a decrease in FVIII activity and purity ([redacted] and [redacted], respectively), demonstrating instability.

Consequently, a shelf-life of 36 months has been proposed for the drug substance when stored in an EVA copolymer bag at ≤−65°C.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a lyophilized formulation for injection containing 250, 500, 1000, 1500, 2000, 2500, or 3000 International Units (IU) of the active ingredient per vial. The drug product contains L-histidine, calcium chloride hydrate, sodium chloride, purified sucrose, polysorbate 80, and hydrochloric acid as excipients. The primary packaging is a 6- or 10-mL glass vial with a bromobutyl rubber stopper, and the secondary packaging is a paper carton.

A prefilled glass vial of 2.5 or 5 mL sterile water for injection in containers (Japanese Pharmacopoeia [JP]) as the reconstitution diluent is supplied with the drug product.

2.2.2 Manufacturing process

The manufacturing process of the drug product consists of the following steps: bulk product solution preparation and sterile filtration, filling, lyophilization, stoppering and capping, labeling and packaging, and storage and testing. Bulk product solution preparation and [redacted], [redacted], [redacted], [redacted], and [redacted] are defined as critical steps. Process validation of the commercial-scale manufacturing process was carried out.

2.2.3 Manufacturing process development

There was a change in manufacturing process associated with an increase in manufacturing scale during the development of the drug product. Comparability between pre-change and post-change formulations has been confirmed in terms of drug product quality attributes (pre-change and post-change manufacturing processes are defined as Process (a) and Process (b), respectively).

The drug product used in the phase I/III study was manufactured by Process (a) or (b), and that used in the phase III study was manufactured by Process (b) [see Sections "7.1 Phase I/III study" and "7.2 Phase III study"].

A QbD approach was used for manufacturing process development [see Section "2.3 QbD"].

2.2.4 Control of drug product

The proposed specifications for the drug product consist of strength, description, identification ([redacted]), [redacted], [redacted], purity (Related Substance 1 [redacted], [redacted] [redacted]), [redacted], bacterial endotoxins, uniformity of dosage units, foreign insoluble matter, insoluble particulate matter, sterility, [redacted], [redacted], and [redacted] ([redacted], [redacted], [redacted], [redacted], [redacted]). [redacted] ([redacted], [redacted], [redacted], [redacted], [redacted]) was included in the proposed specifications during the review.

2.2.5 Stability of drug product

The 250, 500, 1000, 1500, 2000, 2500, and 3000 IU formulations contain the same excipients in the same proportion and the same active ingredient in different strengths. Stability studies were conducted for this application using a bracketing approach where the 250- and 3000-IU formulations manufactured on a commercial scale were placed at the ends from the viewpoint of stability.

Table 4 outlines the major stability studies of the drug product.

Table 4. Outline of major stability studies of the drug product

	Number of batches tested	Storage conditions	Study period	Storage container
Long-term	250 IU: 4 batches 500 IU: 4 batches 1000 IU: 3 batches 2000 IU: 3 batches 3000 IU: 3 batches	5 ± 3°C	36 months	A glass vial with a bromobutyl rubber stopper
	1500 IU: 4 batches 2500 IU: 1 batch		24 months (ongoing)	
Accelerated	250 IU: 3 batches 500 IU: 3 batches 1000 IU: 3 batches 2000 IU: 3 batches 3000 IU: 3 batches	30 ± 2°C, 75 ± 5% RH	12 months	
Post-reconstitution stability	250 IU: 4 batches 500 IU: 1 batch 1000 IU: 2 batches 2000 IU: 2 batches 3000 IU: 2 batches	20°C-25°C	8 hours after reconstitution after storage for 36 months	
Photostability	250 IU: 1 batch	25 ± 2°C, 60 ± 5% RH	Overall illumination: ≥1.2 million lux·h, Integrated near ultraviolet energy: ≥200 W·h/m^2	A glass vial with a bromobutyl rubber stopper (with or without a paper carton)

There were no significant changes in the drug product over time under the long-term conditions and specifications were met throughout the testing period. In the accelerated testing and photostability testing, the drug product showed a decrease in FVIII activity and purity ([redacted] and [redacted], respectively), demonstrating instability. The results of the post-reconstitution stability testing demonstrated that the drug product reconstituted with the supplied diluent is stable for 8 hours at 20°C to 25°C.

Consequently, a shelf-life of 36 months has been proposed for the drug product when stored in a glass vial protected from light at 2°C to 8°C, avoiding freezing.

2.3 QbD

A QbD approach was used for the development of the drug substance and the drug product, and quality control strategies have been established. Based on the quality attributes of the drug product including product-related substances, product-related impurities, and process-related impurities, the following critical quality attributes (CQAs) have been identified. The quality attributes of the drug product have been controlled by combinations of process parameters, in-process controls, and specifications.

- CQAs of the drug substance: [redacted], [redacted], [redacted], and [redacted] (SDS-PAGE), purity ([redacted], [redacted], and [redacted]), [redacted] ([redacted], [redacted]), process-related impurities (bacterial endotoxins, [redacted], Impurity 2, Impurity 12, Impurity 13, and Impurity 8), and viral safety
- CQAs of the drug product: [redacted], [redacted], [redacted], [redacted], purity ([redacted], [redacted]), process-related impurities (bacterial endotoxins, sterility), [redacted], [redacted], and [redacted]

2.R Outline of the review conducted by PMDA

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

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

As data on lonoctocog alfa, the results from primary pharmacodynamic studies (*in vitro* studies in rat and monkey plasma and *in vivo* studies in FVIII knockout [KO] mice, a hemophilia A animal model, [*Haemophilia.* 2008;14:248-59]) and the results from safety pharmacology studies in rats, monkeys, and dogs were submitted.

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies

3.1.1.1 Thrombin generation study in rat plasma (CTD 4.2.1.1-1, Study IVR [redacted]-03)

The hemostatic effect of lonoctocog alfa was evaluated in a thrombin generation assay (TGA), in which lonoctocog alfa was added to the plasma of female rats so that its concentration in plasma

became 1, 3, 10, or 30 IU/mL. Plasma added with the diluent vehicle for lonoctocog alfa was used as the negative control. The results showed that the larger the amount of lonoctocog alfa that was added to plasma, the higher the peak value of thrombin became, demonstrating the thrombin generation potential of lonoctocog alfa.

3.1.1.2 Thrombin generation study in monkey plasma (CTD 4.2.1.1-2, Study IVX [redacted]-10)

The hemostatic effect of lonoctocog alfa was evaluated in a TGA, in which lonoctocog alfa was added to the plasma of female cynomolgus monkeys so that its concentration in plasma became 1, 3, 10, or 30 IU/mL. Plasma added with the diluent vehicle for lonoctocog alfa was used as the negative control. The results showed that the larger the amount of lonoctocog alfa that was added to plasma, the higher the peak value of thrombin became, demonstrating the thrombin generation potential of lonoctocog alfa.

3.1.2 *In vivo* studies

3.1.2.1 Thromboelastography/thromboelastometry and thrombin generation study in blood coagulation factor VIII knockout mice (CTD 4.2.1.1-3, Study PSM [redacted]-18)

The pharmacological effect of lonoctocog alfa was evaluated in blood coagulation factor VIII knockout mice (FVIII KO mice) (a total of 10-11 male and female mice/group) that received a single intravenous dose of lonoctocog alfa (20 IU/kg), Advate (20 IU/kg) as positive control, or the vehicle for lonoctocog alfa as negative control. Based on the results of a thromboelastography (TEG)/ thromboelastometry (TEM) performed using whole blood collected 15 minutes after administration and of a TGA performed using plasma collected 15 minutes after administration, the applicant explained that obvious blood coagulation and thrombin generation were observed in mice receiving lonoctocog alfa or Advate compared with those receiving the vehicle and that the pharmacological effect of lonoctocog alfa was similar to that of Advate.

3.1.2.2 Evaluation of activated partial thromboplastin time in FVIII KO mice (CTD 4.2.1.1-4, Study PSM [redacted]-23)

The pharmacological effect of lonoctocog alfa was evaluated in FVIII KO mice (a total of 10-16 male and female mice/group) that received a single intravenous dose of lonoctocog alfa (20 IU/kg), Advate (20 IU/kg) as positive control, or the vehicle for lonoctocog alfa as negative control. The activated partial thromboplastin time (aPTT) (mean ± standard deviation) measured 15 minutes after administration in the lonoctocog alfa group, Advate group, and vehicle group was 44.6 ± 7.3, 40.8 ± 2.5, and 57.9 ± 12.7 seconds, respectively. Based on the above results, the applicant explained that a decrease in aPTT was observed after administration of lonoctocog alfa or Advate and that the pharmacological effect of lonoctocog alfa was similar to that of Advate.

3.1.2.3 Evaluation of hemostatic effect in FVIII KO mice (CTD 4.2.1.1-6, Studies ABM 03[redacted] and ABM 01[redacted])

A single intravenous dose of lonoctocog alfa (at 1, 5, 15, 40, 100, or 150 IU/kg) or the vehicle for lonoctocog alfa as negative control was administered to FVIII KO mice (a total of 10-40 male and female mice/group) to examine whether there was a dose response relationship for the hemostatic effect of lonoctocog alfa. The caudal extremity was cut off 15 minutes after administration. The proportion of animals that achieved hemostasis by 30 minutes after transection and total amount of blood loss, and aPTTs at 30 minutes after transection were determined. Based on the results, which are shown in Table 5, the applicant explained that a dose-dependent tendency was observed for all endpoints.

Table 5. Evaluation of hemostatic effect in FVIII KO mice

	Dose of lonoctocog alfa (IU/kg)						
	0 (vehicle)	1	5	15	40	100	150
Proportion of animals achieving hemostasis (Number of animals achieving hemostasis/Total number of animals)	13% (5/40)	0% (0/10)	20% (2/10)	65% (13/20)	70% (14/20)	65% (13/20)	80% (8/10)
Total amount of blood loss (μL)[a]	649 ± 285	608 ± 185	528 ± 285	283 ± 370	213 ± 326	158 ± 189	145 ± 240
aPTT (sec)[a]	68 ± 29	68 ± 12	54 ± 9	48 ± 8	46 ± 7	43 ± 7	34 ± 4

a mean ± standard deviation

3.2 Safety pharmacology

The effects of lonoctocog alfa observed on the central nervous system, cardiovascular system, and respiratory system are summarized in Table 6. The study drug was administered intravenously in all of these studies.

Table 6. Summary of safety pharmacology studies

Item	Test system	Endpoint, evaluation method, etc.	Dose	Findings	CTD
Central nervous system	Rat (n = 6/sex/group)	Neurobehavioral assessment	50, 250, 1250 IU/kg	No lonoctocog alfa-related effects on the central nervous system	4.2.1.3-1[b]
Cardiovascular system	Monkey (n = 4/sex/group)	Blood pressure, heart rate, electrocardiogram, etc.	50, 150, 500 IU/kg	No lonoctocog alfa-related effects on the cardiovascular system	4.2.1.3-2[b]
	Dog (n = 4 males/group)		1550 IU/kg[a]		4.2.1.3-3
	Dog (n = 1 male/group)		1550 IU/kg[a]		4.2.1.3-4
	Monkey (n = 2/sex/group)		1550 IU/kg[a]		4.2.1.3-5
Respiratory system	Dog (n = 4 males/group)	Respiratory rate, tidal volume, minute volume	1550 IU/kg[a]	No lonoctocog alfa-related effects on the respiratory system	4.2.1.3-3

a Cumulative dose
b Evaluated in repeated-dose toxicity studies [see Section "5.2 Repeated-dose toxicity"].

3.R Outline of the review conducted by PMDA

Based on the submitted primary pharmacodynamic study data, PMDA considers that lonoctocog alfa has FVIII activity and is expected to be effective in hemostasis *in vivo*. Based on the submitted safety pharmacology study data, PMDA considers that there are no particular safety concerns with lonoctocog alfa.

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

As data on the pharmacokinetics of lonoctocog alfa, the results of studies in cynomolgus monkeys and FVIII KO mice were submitted. FVIII activity levels in plasma samples were determined by a synthetic substrate assay in cynomolgus monkeys and by a synthetic substrate assay and a one-stage clotting assay in FVIII KO mice.

4.1 Absorption

Concerning absorption of lonoctocog alfa, the results of the following studies in cynomolgus monkeys and FVIII KO mice were submitted. Based on these study data, the applicant discussed that the pharmacokinetics of lonoctocog alfa was not markedly different from that of any of the other existing recombinant FVIII products such as Advate.

4.1.1 Single-dose studies

4.1.1.1 Single-dose study in cynomolgus monkeys (CTD 4.2.2.2-2, Study APQ0015)

A single intravenous dose of lonoctocog alfa, Helixate®, or ReFacto AF® (both were recombinant FVIII products unapproved in Japan) was administered at 250 IU/kg to cynomolgus monkeys (n = 1/sex/group). The plasma FVIII activity levels were determined in samples obtained at baseline and 8 time points post-dose between 15 minutes and 24 hours. The pharmacokinetic parameters are shown in Table 7.

Table 7. Pharmacokinetic parameters in cynomolgus monkeys (geometric mean[a])

Study drug		n	C_{max} (IU/mL)	AUC (IU·h/mL)	V_{ss} (mL/kg)	CL (mL/h/kg)	$t_{1/2}$ (h)
Lonoctocog alfa	250 IU/kg	2	11.31	125	26.6	2.00	9.7
Helixate®	250 IU/kg	2	13.50	74	28.5	3.39	6.8
ReFacto AF®	250 IU/kg	2	11.34	93	32.7	2.68	9.6

a Only geometric mean values are presented because each study drug was tested in 2 animals only.

4.1.1.2 Single-dose study in cynomolgus monkeys (CTD 4.2.2.2-3, Study APQ0020)

A single intravenous dose of lonoctocog alfa or Advate was administered at 250 IU/kg to cynomolgus monkeys (n = 1/sex/group). The plasma FVIII activity levels were determined in samples obtained at baseline and 8 time points post-dose between 15 minutes and 24 hours. The pharmacokinetic parameters are shown in Table 8.

Table 8. Pharmacokinetic parameters in cynomolgus monkeys (mean)

Study drug		n	C_{max} (IU/mL)	AUC (IU·h/mL)	CL (mL/h/kg)	$t_{1/2}$ (h)
Lonoctocog alfa	250 IU/kg	2	7.69	95[a]	2.64[a]	10.1[a]
Advate	250 IU/kg	2	8.72	52	4.87	4.7

Only mean values are presented because each study drug was tested in 2 animals only.

a Because the exact pharmacokinetic parameter value failed to be obtained from 1 of the 2 animals, only the result from the other animal is presented.

4.1.1.3 Single-dose study in FVIII KO mice (CTD 4.2.2.2-1, Study PSM 06[redacted])

A single intravenous dose of lonoctocog alfa, Helixate®, ReFacto AF®, or Advate was administered to FVIII KO mice (n = 5 males or females/time point) to estimate the clinical dose of lonoctocog alfa through a pharmacokinetic comparison with other FVIII products. The plasma FVIII activity levels were determined in samples obtained at 10 time points post-dose between 5 minutes and 72 hours. The pharmacokinetic parameters are shown in Table 9.

Table 9. Pharmacokinetic parameters in FVIII KO mice (point estimate)

FVIII activity level determination method	Study drug	Dose[a]	n/time point	C_{max} (IU/mL)	AUC (IU·h/mL)	CL (mL/h/kg)	$t_{1/2}$ (h)
Synthetic substrate assay	lonoctocog alfa	218.6 IU/kg	5	2.31	37	2.74	15
	Helixate®	99.4 IU/kg	5	3.12	32	3.11	15
	ReFacto AF®	110.5 IU/kg	5	2.22	34	2.91	12
	Advate	84.5 IU/kg	5	2.21	18	5.53	8
One-stage clotting assay	lonoctocog alfa	100 IU/kg	5	3.51	55	1.82	16
	Helixate®	100 IU/kg	5	4.30	47	2.11	14
	ReFacto AF®	100 IU/kg	5	2.66	33	3.03	13
	Advate	100 IU/kg	5	2.78	28	3.53	13

a Because FVIII activity levels determined by a synthetic substrate assay were not the same as those determined by a one-stage clotting assay, the doses calculated for each assay are presented. The pharmacokinetic parameters were calculated after correcting plasma FVIII activity levels so that the parameters could show the results in each study drug administered at the same dose in both assays.

4.2 Distribution

Lonoctocog alfa, a recombinant FVIII analog to be administered intravenously, is thought to be distributed primarily in blood similarly to other endogenous FVIIIs; therefore, no studies on distribution have been conducted.

4.3 Metabolism

Lonoctocog alfa, a recombinant protein, is supposed to be metabolized to peptides and amino acids; therefore, based on ICH-S6 (R1), no studies on metabolism have been conducted.

4.4 Excretion

Lonoctocog alfa, a recombinant protein, is supposed to be excreted after being metabolized to peptides and amino acids; therefore, based on ICH-S6 (R1), no studies on excretion have been conducted.

4.R Outline of the review conducted by PMDA

Based on the submitted data from pharmacokinetic studies, PMDA considers that the pharmacokinetics of lonoctocog alfa is not markedly different from that of existing FVIII without modification aimed at extending half-life.

PMDA considers it is acceptable that the applicant has not conducted any studies on the distribution, metabolism, or excretion of lonoctocog alfa.

5. Toxicity and Outline of the Review Conducted by PMDA

The results from the following toxicity studies were submitted as evaluation data on the toxicity of lonoctocog alfa: single-dose toxicity studies, repeated-dose toxicity studies, a local tolerance study, and a thrombogenicity study.

5.1 Single-dose toxicity

5.1.1 Single intravenous dose toxicity study in rats (CTD 4.2.3.1-1, Study APQ0010)

SD rats (n = 5/sex/group) received a single intravenous dose of lonoctocog alfa at 0 (saline), 50, 250, or 1500 IU/kg (approximately 7.5-fold the maximum clinical dose) and were observed for 5 days. No deaths or toxic changes that were considered attributable to lonoctocog alfa were observed in any group. Based on the above, the no observed adverse effect level (NOAEL) and the approximate lethal dose were determined to be 1500 IU/kg and >1500 IU/kg, respectively.

5.1.2 Single intravenous dose toxicity study in cynomolgus monkeys (CTD 4.2.3.1-2, Study APQ0011)

Cynomolgus monkeys (n = 3/sex/group) received a single intravenous dose of lonoctocog alfa at 0 (saline), 50, 250, or 1500 IU/kg (approximately 7.5-fold the maximum clinical dose) and were observed for 11 days. No deaths or toxic signs that were considered attributable to lonoctocog alfa were observed in any group. Based on the above, the NOAEL and the approximate lethal dose were determined to be 1500 IU/kg and >1500 IU/kg, respectively.

5.2 Repeated-dose toxicity

5.2.1 Four-week intravenous dose toxicity study in rats with a 2-week reversibility period (CTD 4.2.1.3-1, Study APQ0013)

Lonoctocog alfa was administered intravenously to SD rats daily at 0 (saline), 50, 250, or 1250 IU/kg/day (approximately 6.25-fold the maximum clinical dose) for 5 days (animals for interim necropsy: n = 5/sex/group) or 4 weeks (n = 15/sex/group for the 0 and 1250 IU/kg/day groups, n = 10/sex/group for the 50 and 250 IU/kg/day groups). After a 2-week recovery period following a 4-week administration period, reversibility was evaluated in 5 male and 5 female animals each in the 0 and 1250 IU/kg/day groups. No deaths were observed in either group. While no toxic changes that were considered attributable to lonoctocog alfa were observed, production of antibodies to lonoctocog

alfa, a foreign protein to animals, was identified, and the plasma concentrations of lonoctocog alfa on Day 28 were less than the detection limit (0.5 IU/mL) or equivalent (up to 0.65 IU/mL). On Day 28, a mild prolongation of aPTT was observed in male and female animals in the 1250 IU/kg/day group, which was likely to be attributable to cross reactivity between antibodies to lonoctocog alfa and endogenous FVIII in rats. Based on the above, the NOAEL was determined to be 1250 IU/kg.

5.2.2 Four-week intravenous dose toxicity study in cynomolgus monkeys (CTD 4.2.1.3-2, Study APQ0014)

Lonoctocog alfa was administered intravenously daily to cynomolgus monkeys at 0 (saline), 50, 150, or 500 IU/kg/day (approximately 2.5-fold the maximum clinical dose) for 5 days (animals for interim necropsy: n = 1/sex/group) or 4 weeks (n = 3/sex/group). No deaths were observed in any group. While no toxic changes that were considered attributable to lonoctocog alfa were observed, production of antibodies to lonoctocog alfa, a foreign protein to animals, was identified, and the plasma concentrations of lonoctocog alfa on Day 28 were lower than those on Day 1. In ≥150 IU/kg groups, a mild prolongation of aPTT was observed in Week 2 or later, which was likely to be attributable to cross reactivity between antibodies to lonoctocog alfa and endogenous FVIII in cynomolgus monkeys. Also for transient tremor observed in ≥150 IU/kg groups as a change in clinical signs on Day 6 or later, a relationship with the activation of the immune system induced by antibody reaction was suggested. Based on the above, the NOAEL was determined to be 500 IU/kg.

5.3 Genotoxicity

Lonoctocog alfa is an analog of a plasma protein present in the human body and is unlikely to have genotoxicity; therefore, no genotoxicity studies have been conducted.

5.4 Carcinogenicity

Lonoctocog alfa is an analog of a plasma protein present in the human body and is unlikely to have carcinogenicity; therefore, no carcinogenicity studies have been conducted.

5.5 Reproductive and developmental toxicity

Considering that a relationship between a hypercoagulation state during pregnancy and miscarriage or placenta-mediated complications has been suggested (*Nat Rev Rheumatol.* 2011;7:330-9; *Obstet Gynecol.* 2007;109:1146-55) and that it is difficult to evaluate reproductive and developmental toxicity correctly in normal animals receiving a high dose of lonoctocog alfa, no reproductive and developmental toxicity studies have been conducted. In single- and repeated-dose toxicity studies in rats and cynomolgus monkeys [see Sections “5.1 Single-dose toxicity” and “5.2 Repeated-dose toxicity”], no lonoctocog alfa-related changes were detected in male or female reproductive organs.

5.6 Local tolerance

5.6.1 Single intravenous, intraarterial, or perivenous dose local tolerance study in rabbits (CTD 4.2.3.6-1, Study APQ 0012)

New Zealand White (NZW) rabbits (n = 3 males/group) received 1 mL of lonoctocog alfa (359 IU/mL) or saline intravenously or intraarterially, or 0.2 mL of either agent perivenously. No lonoctocog alfa-related local irritation was observed.

5.7 Other toxicity studies

5.7.1 *In vivo* thrombogenicity study in rabbits (CTD 4.2.3.7.3-1, Study S30668)

Lonoctocog alfa was administered intravenously to NZW rabbits (n = 3/sex/group) at 150, 300, 500, or 1000 IU/kg. Saline (negative control), Feiba 200 IU/kg (positive control), or ReFacto AF® (a recombinant FVIII product unapproved in Japan) 500 IU/kg was administered to rabbits (n = 6/sex/group). Thrombogenicity was evaluated using the modified method of Wessler model of venous congestion (*Thromb Res.* 1980;17:353-66). Thrombogenicity was observed only in the lonoctocog alfa 1000 IU/kg group and the positive control groups. Based on the above, the NOAEL for thrombogenicity was determined to be 500 IU/kg.

5.R Outline of the review conducted by PMDA

PMDA concluded that there are no particular problems with the toxicological evaluation of lonoctocog alfa.

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

6.1.1 Methods to determine plasma FVIII activity levels

Plasma FVIII activity levels were determined by a synthetic substrate assay and a one-stage clotting assay.

6.1.2 Results of synthetic substrate assay and one-stage clotting assay

It has been reported that FVIII activity levels of recombinant FVIII products determined by a one-stage clotting assay tend to be lower than those determined by a synthetic substrate assay (*Br. J. Haematol.* 2002;117:957-60; *Haematophilia.* 2011;17:695-702). Taking account of this, concerning plasma FVIII activity after administration of lonoctocog alfa in Part 1 of Study 1001 [see Section "6.2.1.1 Global phase I/III study"], a comparison was made between the levels determined by a synthetic substrate assay and those determined by a one-stage clotting assay. As a result, the plasma FVIII activity levels determined by a one-stage clotting assay were approximately half of those determined by a synthetic substrate assay. Similarly, it was found that the plasma FVIII activity levels in Part 3 of Study 1001 and Study 3002 [see Section "6.2.1.2 Foreign phase III study"] determined by

a one-stage clotting assay were consistently lower (approximately half) than those determined by a synthetic substrate assay.

The above results suggested that FVIII activity levels of lonoctocog alfa may be underestimated when determined using a one-stage clotting assay. Therefore, the applicant explained that they will appropriately provide the following information in the package insert and other relevant materials: Plasma FVIII activity levels, if monitored using a one-stage clotting assay, should be corrected.

6.2 Clinical pharmacology

As the evaluation data for clinical pharmacology, the results from a global phase I/III study (CTD 5.3.5.1-1, Study 1001) and a foreign phase III study (CTD 5.3.5.2-1, Study 3002), and the results from a population pharmacokinetic analysis (CTD 5.3.3.5-1) performed using data from these 2 studies were submitted.

6.2.1 Study in patients

6.2.1.1 Global phase I/III study (CTD 5.3.5.1-1, Study 1001 [[redacted] 20[redacted] to [redacted] 20[redacted]])

In Part 1 of this study, 27 subjects with severe hemophilia A (<1% FVIII activity) aged ≥18 and ≤65 years with no inhibitors who previously received treatment with other FVIII products (>150 exposure days to FVIII products) first received a single intravenous dose of Advate at 50 IU/kg; then underwent a 4-day washout period; and finally received a single intravenous dose of lonoctocog alfa at the same dose as that of Advate. The plasma FVIII activity levels were determined in samples obtained at baseline and at a total of 10 time points after administration of each study drug (0.5-72 hours post-dose). The pharmacokinetic parameters of lonoctocog alfa and Advate are shown in Table 10. Concerning the pharmacokinetic parameters calculated based on FVIII activity levels determined by a synthetic substrate assay, the applicant explained that AUC, CL, and $t_{1/2}$ after administration of lonoctocog alfa were greater, lower, and longer, respectively, than the corresponding parameters after administration of Advate.

Table 10. Pharmacokinetic parameters of lonoctocog alfa and Advate (mean ± standard deviation)

	Synthetic substrate assay		One-stage clotting assay	
	Lonoctocog alfa (n = 27)	Advate (n = 27)	Lonoctocog alfa (n = 27)	Advate (n = 27)
IR[a] [(IU/dL)/(IU/kg)]	2.24 ± 0.36	2.73 ± 0.45	1.06 ± 0.18	2.09 ± 0.42
C_{max}[a] (IU/dL)	113 ± 17	137 ± 21	55 ± 8	105 ± 21
$AUC_{0-\infty}$ (h·IU/dL)	2090 ± 650	1820 ± 647	1310 ± 451	2060 ± 725
CL (mL/h/kg)	2.64 ± 0.85	3.14 ± 1.20	4.26 ± 1.45	2.76 ± 1.06
V_{ss} (mL/kg)	50 ± 8	49 ± 10	90 ± 14	51 ± 11
$t_{1/2}$ (h)	14.5 ± 3.8	13.3 ± 4.4	15.4 ± 4.9	13.9 ± 4.4
MRT (h)	20.4 ± 5.5	17.1 ± 5.6	23.0 ± 7.4	20.2 ± 6.3

a Value corrected by subtracting a baseline FVIII activity level from a post-dose FVIII activity level

In Part 3 of this study, the pharmacokinetics of lonoctocog alfa was evaluated in 64 subjects (including 10 Japanese subjects) with severe hemophilia A (<1% FVIII activity) aged ≥12 and ≤65 years with no

inhibitors who previously received treatment with other FVIII products (>150 exposure days to FVIII products). A single intravenous dose of lonoctocog alfa at 50 IU/kg was administered, and plasma FVIII activity levels were determined in samples obtained at baseline and at a total of 12 time points after administration (10 minutes to 96 hours post-dose). The pharmacokinetic parameters are shown in Table 11. The applicant explained that the pharmacokinetic parameters in Japanese subjects were similar to those in non-Japanese subjects.

Table 11. Pharmacokinetic parameters of lonoctocog alfa in Japanese and non-Japanese subjects (mean ± standard deviation)

	Synthetic substrate assay		One-stage clotting assay	
	Japanese (n = 10)	Non-Japanese (n = 54)	Japanese (n = 10)	Non-Japanese (n = 54)
IR[a] [(IU/dL)/(IU/kg)]	2.07 ± 0.23	1.81 ± 0.42	0.85 ± 0.16	0.84 ± 0.19
C_{max}[a] (IU/dL)	109 ± 13	98 ± 21	46 ± 4	46 ± 9
$AUC_{0-\infty}$ (h·IU/dL)	2060 ± 327	1790 ± 676	1210 ± 252	1070 ± 457
CL (mL/h/kg)	2.49 ± 0.43	3.28 ± 1.27	4.30 ± 1.01	5.79 ± 2.69
V_{ss} (mL/kg)	56 ± 11	60 ± 15	103 ± 15	110 ± 26
$t_{1/2}$ (h)	16.4 ± 4.8	13.7 ± 3.5	16.0 ± 3.8	14.2 ± 4.1
MRT (h)	23.0 ± 5.8	19.9 ± 5.2	25.1 ± 6.5	21.4 ± 6.3

a Value corrected by subtracting a baseline FVIII activity level from a post-dose FVIII activity level

Furthermore, out of the 64 subjects who underwent pharmacokinetic evaluation in Part 3, the pharmacokinetics of lonoctocog alfa after administration at 50 IU/kg was evaluated, similarly to the initial administration, in 30 subjects (including 8 Japanese subjects) who had received on-demand or prophylactic treatment with lonoctocog alfa for 3 to 6 months. The applicant explained that the pharmacokinetic parameters of lonoctocog alfa after the initial dose were similar to those after multiple doses and that the impact of multiple doses, such as a decrease in exposure, was not seen in any pharmacokinetic findings of lonoctocog alfa.

6.2.1.2 Foreign phase III study (CTD 5.3.5.2-1, Study 3002 [redacted] 20[redacted] to [redacted] 20[redacted])

The pharmacokinetics of lonoctocog alfa was evaluated in 39 subjects with severe hemophilia A (<1% FVIII activity) aged ≥0 and <12 years with no inhibitors who previously received treatment with other FVIII products (>50 exposure days to FVIII products). A single intravenous dose of lonoctocog alfa was administered to subjects at 50 IU/kg, and the plasma FVIII activity levels were determined in samples obtained at baseline and at a total of 5 time points after administration (1-48 hours post-dose). The pharmacokinetic parameters are shown in Table 12. The applicant explained that the pharmacokinetic parameters in subjects aged <6 years were similar to those aged ≥6 and <12 years and that CL and $t_{1/2}$ in these subjects tended to be higher and shorter, respectively, than the corresponding parameters in subjects aged ≥12 and ≤65 years in Study 1001.

Table 12. Pharmacokinetic parameters in children aged <12 years (mean ± standard deviation)

	Synthetic substrate assay		One-stage clotting assay	
	≥0 and <6 years (n = 20)	≥6 and <12 years (n = 19)	≥0 and <6 years (n = 20)	≥6 and <12 years (n = 19)
IR[a] [(IU/dL)/(IU/kg)]	1.60 ± 0.34	1.66 ± 0.33	0.87 ± 0.73	0.84 ± 0.17
C_{max}[a] (IU/dL)	80 ± 17	84 ± 16	44 ± 36	42 ± 9
$AUC_{0-\infty}$ (h·IU/dL)	1080 ± 334	1170 ± 307	610 ± 379	683 ± 227
CL (mL/h/kg)	5.1 ± 1.5	4.6 ± 1.4	10.8 ± 6.3	8.4 ± 3.6
V_{ss} (mL/kg)	71 ± 8	67 ± 15	142 ± 51	121 ± 26
$t_{1/2}$ (h)	10.4 ± 3.0	10.2 ± 2.0	10.9 ± 5.3	10.3 ± 2.7
MRT (h)	12.4 ± 3.1	12.3 ± 2.1	12.2 ± 3.9	12.8 ± 2.3

a Value corrected by subtracting a baseline FVIII activity level from a post-dose FVIII activity level

6.2.2 Population pharmacokinetic analysis (CTD 5.3.3.5-1)

A population pharmacokinetic analysis (NONMEM version 7.2) was conducted using plasma FVIII activity data obtained from a total of 1460 samples collected in the global phase I/III study (Study 1001) and the foreign phase III study (Study 3002). This analysis was based on a 2-compartment model, and various candidate factors were evaluated as covariates for the pharmacokinetic profile of lonoctocog alfa. As a result, a 2-compartment model was chosen as the final model with body weight and baseline vWF as covariates. Using this model, plasma FVIII activity levels after repeated administration were simulated. The trough values estimated from the simulation are shown in Table 13. The median plasma FVIII activity trough level was estimated to be higher than 1% (1 IU/dL) after administration at any dose or frequency. Therefore, the applicant explained that the proposed dosage and administration of lonoctocog alfa for routine prophylaxis, “20 to 50 IU per kg administered 2 or 3 times weekly,” is appropriate.

Table 13. Plasma FVIII activity trough levels (IU/dL) estimated by simulation (median [90% prediction interval])[a]

Dosing frequency (dosing day)	Simulated day	Dose			
		20 IU/kg	30 IU/kg	40 IU/kg	50 IU/kg
Every 2 days		3.2 [0.9, 10.4]	4.2 [1.1, 15.0]	5.3 [1.3, 19.6]	6.4 [1.4, 24.3]
Every 3 days		1.5 [0.5, 4.8]	1.8 [0.6, 6.5]	2.0 [0.6, 8.4]	2.3 [0.7, 10.2]
Twice weekly (Days 0 and 3)	Day 3 Day 7	1.5 [0.5, 4.6] 1.1 [0.4, 3.0]	1.8 [0.6, 6.2] 1.2 [0.4, 3.7]	2.0 [0.6, 7.9] 1.2 [0.4, 4.4]	2.3 [0.6, 9.6] 1.3 [0.5, 5.2]
Twice weekly (Days 0 and 3.5)	Day 3.5 Day 7	1.2 [0.4, 3.6] 1.2 [0.4, 3.6]	1.4 [0.5, 4.6] 1.4 [0.5, 4.6]	1.5 [0.5, 5.8] 1.5 [0.5, 5.8]	1.7 [0.5, 7.0] 1.7 [0.5, 7.0]
3 times weekly (Days 0, 2, and 4)	Day 2 Day 4 Day 7	3.0 [0.9, 8.7] 3.1 [0.9, 9.9] 1.5 [0.6, 5.2]	4.0 [1.1, 12.5] 4.2 [1.1, 14.3] 1.8 [0.6, 7.2]	5.0 [1.3, 16.3] 5.3 [1.3, 18.7] 2.1 [0.6, 9.3]	6.1 [1.4, 20.1] 6.4 [1.4, 23.2] 2.3 [0.7, 11.3]
3 times weekky (Days 0, 2, and 4.5)	Day 2 Day 4.5 Day 7	3.0 [0.9, 8.7] 2.1 [0.7, 7.0] 2.0 [0.7, 6.8]	4.0 [1.1, 12.5] 2.6 [0.8, 9.9] 2.5 [0.8, 9.6]	5.0 [1.3, 16.3] 3.1 [0.8, 12.9] 3.1 [0.8, 12.4]	6.1 [1.4, 20.1] 3.7 [0.9, 15.9] 3.6 [0.9, 15.3]

a Calculated as the results of measurements by a synthetic substrate assay

6.R Outline of the review conducted by PMDA

Based on the submitted clinical pharmacology data, PMDA considers that there is no marked difference in pharmacokinetic parameters between lonoctocog alfa and Advate. With respect to the appropriateness of the proposed dosage and administration for routine prophylaxis, which should be

discussed taking into account the dosage regimen specified in clinical studies as well as efficacy data, PMDA will discuss in Section "7.R.5 Dosage and administration."

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

As efficacy and safety evaluation data, the results from the global phase I/III study (CTD 5.3.5.1-1, Study 1001) and the foreign phase III study (CTD 5.3.5.2-1, Study 3002) were submitted. These clinical studies are summarized in Table 14.

Table 14. List of clinical studies

	Study No. (Phase)	Subjects	Number of subjects treated	Outline of dosage regimen
Global	1001 (I/III)	Previously treated patients with severe hemophilia A (≥18 and ≤65 years for Part 1 and 2; ≥12 and ≤65 years for Part 3)	27 subjects in Part 1	A single dose (50 IU/kg) each of Advate and lonoctocog alfa, with a 4-day washout period between the 2 doses
			26 subjects[a] in Part 2 Prophylaxis group, 14 subjects On-demand group, 12 subjects 147 subjects in Part 3 Prophylaxis group, 132 subjects On-demand group, 15 subjects	Prophylaxis group Administration of lonoctocog alfa at 20-40 IU/kg every other day, at 20-50 IU/kg 2 or 3 times weekly, or at other doses and dosing intervals On-demand group Administration of lonoctocog alfa in accordance with the recommendation in the World Federation of Hemophilia (WFH) Guidelines
			Perioperative management, 16 cases in 13 subjects	Perioperative management of bleeding Administration of lonoctocog alfa in accordance with the recommendation in the WFH Guidelines
Foreign	3002 (III)	Previously treated patients with severe hemophilia A (≥0 and <12 years)	84 subjects Prophylaxis group, 81 subjects On-demand group, 3 subjects	Prophylaxis group Administration of lonoctocog alfa at 15-50 IU/kg every other day or 2 or 3 times weekly On-demand group Administration of lonoctocog alfa at a dose prescribed by the investigator based on previous treatments

a Subjects treated in Part 1 were transferred into Part 2.

Each clinical study is summarized below. The results of pharmacokinetic analysis in each study are presented in Section "6.2 Clinical pharmacology."

7.1 Phase I/III study

7.1.1 Global phase I/III study (CTD 5.3.5.1-1, Study 1001 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A non-randomized, open-label study was conducted at 54 sites in 20 countries including Japan to assess the safety, efficacy, and pharmacokinetics of lonoctocog alfa in subjects with severe hemophilia A (<1% FVIII activity) aged ≥12 and ≤65 years with no inhibitors who previously received treatment with other FVIII products (>150 exposure days to FVIII products) (target sample size, 26 subjects for Part 1 and Part 2 and 85 subjects for Part 3).

This study comprised 3 parts, and each part was designed as follows:

Part 1: A single dose (50 IU/kg) each of Advate and lonoctocog alfa was administered with a 4-day washout period between the 2 doses to subjects aged ≥18 and ≤65 years to evaluate pharmacokinetics [see Section "6.2.1.1 Global phase I/III study"].

Part 2: Out of subjects completing treatment in Part 1, the first 5 subjects were assigned to the on-demand treatment group (hereinafter referred to as "on-demand group") and the other subjects were assigned to either the routine prophylaxis treatment group (hereinafter referred to as "prophylaxis group") or the on-demand group according to subjects' wishes or at the discretion of the investigator. The prophylaxis group received lonoctocog alfa at 20 to 40 IU/kg every other day, at 20 to 50 IU/kg 2 or 3 times weekly, or at other doses and dosing intervals. The on-demand group received lonoctocog alfa at a dose needed to obtain a sufficient FVIII activity level for hemostasis in accordance with the recommendation in the WFH Guidelines. Subjects in either group were treated for at least 50 exposure days.

Part 3: Subjects aged ≥12 and ≤65 years were assigned to either the prophylaxis group or the on-demand group according to subjects' wishes or at the discretion of the investigator, and received lonoctocog alfa at the same dosage regimen as those used in Part 2. Subjects in either group were treated for at least 50 exposure days.

When any subjects participating in Part 1, 2, or 3 underwent surgery, information of the efficacy and safety of lonoctocog alfa used at the time of surgery was collected (target number of surgical cases, ≥10 cases including ≥5 cases of emergency or elective major surgeries). Lonoctocog alfa was administered before, after, and, if needed, during a surgery in accordance with the recommendation in the WFH Guidelines.

All 174 subjects enrolled in the study (27 in Part 1 and 147 in Part 3 [including 10 Japanese subjects]) received lonoctocog alfa and were included in the safety analysis set. Of those in the safety analysis set, 173 subjects enrolled in Part 2 or 3 (27 in the on-demand group [including 1 Japanese subject] and 146 in the prophylaxis group [including 9 Japanese subjects]), excluding 1 subject withdrawn from the study before starting the study treatment, were included in the efficacy analysis set. Surgery-related information was obtained from 13 subjects undergoing 16 surgeries (including 0 Japanese subjects).

The number of lonoctocog alfa exposure days per subject (mean ± standard deviation) was 44.0 ± 30.5 (range; 5, 132) days for the on-demand group (n = 27) and 89.8 ± 62.8 (range; 1, 395) days for the prophylaxis group.

The primary endpoints in the study were (a) proportion of subjects developing inhibitors against lonoctocog alfa, (b) hemostatic efficacy in on-demand treatment, and (c) annualized spontaneous bleeding rate (AsBR) in routine prophylaxis, which were evaluated in the order of (a), (b), and (c). Only if the pre-specified criterion was met in the evaluation of an endpoint, was the next endpoint evaluated.

The proportion of subjects developing inhibitors against lonoctocog alfa[1] [95% confidence interval (CI)] was 0% (0 of 120 subjects) [0.0, 3.0], and the upper limit of the 95% CI was below the pre-specified threshold (6.8%).

In on-demand treatment, the hemostatic efficacy of lonoctocog alfa for treatment of bleeding episodes was evaluated according to Table 15 and Table 16. The proportion of bleeding episodes for which hemostatic efficacy was rated as "excellent" or "good" [95% CI][2] was 92.3% (783 of 848 episodes) [88.9, 94.8], and the lower limit of the 95% CI was above the pre-specified success threshold (70%). The corresponding proportion in Japanese subjects was 89.7% (26 of 29 episodes).

Table 15. Assessment criteria for the hemostatic efficacy of lonoctocog alfa for treatment of bleeding episodes

Excellent	Obvious pain relief and/or improvement in signs of bleeding (improvement of swelling/tenderness, and/or increased range of motion in the case of musculoskeletal hemorrhage) within approximately 8 hours after the first dose of lonoctocog alfa.
Good	Obvious pain relief and/or improvement in signs of bleeding at approximately 8 hours after the first dose of lonoctocog alfa, but requires 2 doses for complete resolution.
Moderate	Probable or slight beneficial effect within approximately 8 hours after the first dose of lonoctocog alfa; but requires >2 doses for complete resolution.
Poor/No response	No improvement at all or condition worsens (i.e., signs of bleeding) after the first dose of lonoctocog alfa and additional hemostatic intervention is required with another FVIII product, cryoprecipitate, or plasma for complete resolution.

Table 16. Assessment criteria for the hemostatic efficacy of lonoctocog alfa for treatment of major injury or life-threatening bleeds

Excellent	Hemostasis clinically not significantly different from normal in terms of quantity and/or quality (e.g., achieved hemostasis comparable to that expected during similar surgery in a non-factor deficient patient) and estimated blood loss from injury is not more than 20% higher than the predicted blood loss from similar injury or other causes.
Good	Normal or mildly abnormal hemostasis in terms of quantity and/or quality (e.g., slight oozing, prolonged time to hemostasis with somewhat increased bleeding compared to a non-factor deficient patient) or estimated blood loss is 20%-30% higher than the predicted blood loss from similar injury or other causes.
Moderate	Moderately abnormal hemostasis in terms of quantity and/or quality (e.g., moderate hemorrhage that is difficult to control) with estimated blood loss greater than what is defined as "good."
Poor/No response	Severely abnormal hemostasis in terms of quantity and/or quality (e.g., severe hemorrhage that is difficult to control), and/or additional hemostatic intervention is required with another FVIII product, cryoprecipitate, or plasma for complete resolution, exceeding the predicted intervention needed to resolve similar injury or other causes.

For routine prophylaxis, AsBR in the on-demand group and the prophylaxis group was evaluated. The results of evaluation of AsBR are presented in Table 17, showing a significant difference between the prophylaxis group and the on-demand group. The median [range] AsBR in Japanese subjects was 3.55/person-year in the on-demand group (1 subject) and 0.00 [0.0, 13.0]/person-year in the prophylaxis group.

---

1 Number of subjects developing inhibitors / (Number of subjects achieving ≥50 exposure days + Number of subjects achieving <50 exposure days who developed inhibitors)

2 Calculated by generalized estimating equation in consideration of intra-subject correlation

Table 17. Between-group comparison of AsBR (Efficacy analysis set)

	On-demand (n = 27)	Prophylaxis (n = 146)
Number of subjects experiencing spontaneous bleeding episodes requiring treatment	23	54
Number of spontaneous bleeding episodes requiring treatment	460	156
Mean ± standard deviation	24.84 ± 33.84	2.10 ± 4.76
Median [range]	11.73 [0.0, 151.0]	0.00 [0.0, 40.6]
Annual number of bleeding episodes [95% CI][a]	19.5 [17.8, 21.3]	1.6 [1.3, 1.8]
Between-group rate [95% CI][a]	0.08 [0.07, 0.10]	
P-value[a]	<0.0001	

a A generalized linear model based on a Poisson distribution (logarithmic link) with treatment groups as a factor and the logarithm of observation period as an offset variable

For perioperative management of bleeding, hemostatic efficacy of lonoctocog alfa in the perioperative period was evaluated based on a 4-grade rating scale presented in Table 18. Thirteen subjects underwent 16 surgical procedures (5 cases of knee arthroplasty, 3 cases of circumcision, and 1 case each of wisdom teeth removal, abdominal hernia repair, joint arthroplasty, ankle arthroplasty, ligament operation, cholecystectomy, open reduction of fracture, and medical device removal). The treatment success rate (proportion of cases assessed as “excellent” or “good”) was 100% (16 of 16 cases), exceeding the pre-specified threshold (70%).

Table 18. Assessment criteria for the hemostatic efficacy of lonoctocog alfa for preoperative management

Excellent	Hemostasis clinically not significantly different from normal in terms of quantity and/or quality (e.g., achieved hemostasis comparable to that expected during similar surgery in a non-factor deficient patient in the absence of other hemostatic intervention) and estimated blood loss during surgery is not more than 20% higher than the predicted blood loss for the intended surgery.
Good	Normal or mildly abnormal hemostasis in terms of quantity and/or quality (e.g., slight oozing, prolonged time to hemostasis with somewhat increased bleeding compared to a non-factor deficient patient in the absence of other hemostatic intervention) or estimated blood loss is 20%-30% higher than the predicted blood loss for intended surgery.
Moderate	Moderately abnormal hemostasis in terms of quantity and/or quality (e.g., moderate hemorrhage that is difficult to control) with estimated blood loss greater than what is defined as good.
Poor/No response	Severely abnormal hemostasis in terms of quantity and/or quality (e.g., severe hemorrhage that is difficult to control), and/or additional hemostatic intervention is required with another FVIII product, cryoprecipitate, or plasma for complete resolution.

Concerning safety, no deaths or adverse events leading to study discontinuation were observed in Part 1, 2, or 3.

In Part 1, during the observation period which was from the time of study drug administration to 3 days after administration, 3.7% (1 of 27) of subjects receiving Advate experienced 1 adverse event (musculoskeletal pain), and 7.4% (2 of 27) of subjects receiving lonoctocog alfa experienced 2 adverse events (toothache and feeling hot). The outcomes of these adverse events were assessed as resolved. Feeling hot that occurred after administration of lonoctocog alfa was assessed as related to the study drug.

In Parts 2 and 3, 290 adverse events occurred in 64.7% (112 of 173) of subjects. The adverse events that occurred with an incidence of ≥4% in any group are shown in Table 19.

Table 19. Adverse events that occurred with an incidence of ≥4% in any group in Part 2 or 3 (Safety analysis set)

Name of adverse event	On-demand (27 subjects[a])		Prophylaxis (146 subjects[b])	
	Number of subjects (%)	Number of events	Number of subjects (%)	Number of events
Pharyngitis	5 (18.5)	6	13 (8.9)	16
Arthralgia	3[a] (11.1)	3	14 (9.6)	16
Headache	1 (3.7)	1	11 (7.5)	12
Rash	1 (3.7)	1	6 (4.1)	7
Upper respiratory tract infection	0 (0.0)	0	6 (4.1)	6
Toothache	2 (7.4)	2	4 (2.7)	5
Dizziness	2 (7.4)	3	2 (1.4)	2
Injection site pain	2 (7.4)	2	0 (0.0)	0
Anaemia	2 (7.4)	2	0 (0.0)	0

a Including 1 subject for whom treatment was changed from on-demand to prophylaxis during the study period
b Including 1 subject for whom treatment was changed from prophylaxis to on-demand during the study period

The following 19 events of adverse drug reactions occurred in 13 subjects: 2 events of chills and 1 event each of feeling hot, dizziness, injection site pain, and pyrexia in the on-demand group; and 3 events each of hypersensitivity and arthralgia and 1 event each of paraesthesia, joint range of motion decreased, dizziness, erythema, pruritus, drug specific antibody present, and rash in the prophylaxis group. The outcomes of these adverse drug reactions, excluding rash that was assessed as resolving, were all assessed as resolved. As serious adverse events, the following 9 events occurred in 7 subjects: 1 event each of anaemia, thrombocytopenia, and ankle fracture in the on-demand group; and 1 event each of blood uric acid increased, varices oesophageal, tonsillar haemorrhage, hypersensitivity, viral infection, and suicidal ideation in the prophylaxis group. Out of these serious adverse events, for hypersensitivity in the prophylaxis group, a causal relationship with lonoctocog alfa could not be ruled out. The outcomes of all the events were assessed as resolved.

Among Japanese subjects, 20 adverse events occurred in 80.0% (8 of 10) of subjects. One adverse drug reaction (dizziness in the prophylaxis group) occurred in 1 subject, and its outcome was assessed as resolved. No serious adverse events were reported.

7.2 Phase III study

7.2.1 Foreign phase III study (CTD 5.3.5.2-1, Study 3002 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A non-randomized, open-label study was conducted at 37 sites in 19 countries to assess the efficacy, safety, and pharmacokinetics of lonoctocog alfa in subjects with severe hemophilia A (<1% FVIII activity) aged ≥0 and <12 years with no inhibitors who previously received treatment with other FVIII products (>50 exposure days to FVIII products) (target sample size, 55 subjects [changed to approximately 75 subjects during the study]).

Subjects enrolled in this study were assigned to either the prophylaxis group or the on-demand group according to subjects' (or their guardians') wishes or at the discretion of the investigator. The

prophylaxis group received lonoctocog alfa at 15 to 50 IU/kg every other day or 2 or 3 times weekly. The on-demand group received lonoctocog alfa at a dose prescribed by the investigator based on a dose administered to treat previous bleeding episodes so that a sufficient FVIII activity level for hemostasis was obtained in accordance with the recommendation in the WFH Guidelines. The study drug was administered until when at least 25 subjects in each age group (≥0 and <6 years, ≥6 and <12 years) achieved 50 exposure days to lonoctocog alfa. The pharmacokinetics of lonoctocog alfa after administration at 50 IU/kg was evaluated in some subjects [see Section "6.2.1.2 Foreign phase III study"].

All 84 subjects enrolled in the study (35 subjects aged ≥0 and <6 years [all in the prophylaxis group] and 49 subjects aged ≥6 and <12 years [3 in the on-demand group and 46 in the prophylaxis group]) were included in the safety analysis set. Of these, 83 subjects, excluding 1 subject who was reported to be negative for FVIII inhibitors at screening and turned positive during the study, were included in the efficacy analysis set.

The number of exposure days to lonoctocog alfa per subject (mean ± standard deviation) was 50.7 ± 21.7 [range; 26, 67] days for the on-demand group and 62.8 ± 25.0 [range; 4, 142] days for the prophylaxis group. Twenty-seven subjects aged ≥0 and <6 years and 38 subjects aged ≥6 and <12 years achieved >50 exposure days.

With respect to efficacy in control of bleeding, the primary endpoint, the proportion of bleeding episodes for which the hemostatic efficacy rating was either "excellent" or "good" based on the 4-grade scale presented in Table 15 and Table 16 was 96.3% (334 of 347 episodes).

Concerning efficacy in routine prophylaxis, a secondary endpoint, the median AsBR [range] was 0.00 [0.0, 14.0]/person-year for the prophylaxis group and 31.76 [0.0, 42.7]/person-year for the on-demand group.

The safety data show 183 adverse events in 76.2% (64 of 84) of subjects. The adverse events that occurred in ≥4 subjects are shown in Table 20.

Table 20. Adverse events that occurred in ≥4 subjects (Safety analysis set, 84 subjects)

Name of adverse event	Number of subjects (%)	Number of events
Pharyngitis	14 (16.7)	15
Arthralgia	8 (9.5)	8
Cough	7 (8.3)	10
Headache	7 (8.3)	9
Head injury	5 (6.0)	6
Pyrexia	5 (6.0)	5
Upper respiratory tract infection	4 (4.8)	5
Rhinitis	4 (4.8)	4
Fall	4 (4.8)	4
Pain in extremity	4 (4.8)	4

During the study period, 9 subjects experienced 11 serious adverse events (3 events of anaemia, and 1 event each of laceration, device occlusion, dyspepsia, bacteraemia, pneumonia, systemic inflammatory response syndrome, hand fracture, and splenic rupture) and 1 subject experienced 1 adverse event leading to study discontinuation (arthralgia). All these events were assessed as not related to lonoctocog alfa, and their outcomes were all assessed as resolved. As an adverse drug reaction, 1 subject experienced 1 event of non-serious hypersensitivity, the outcome of which was assessed as resolved. No deaths occurred during the study period.

7.R Outline of the review conducted by PMDA

7.R.1 Review policy

7.R.1.1 Efficacy and safety evaluation

There is no apparent difference in patients with FVIII deficiency including hemophilia A between Japan and other countries in terms of their epidemiological characteristics, status of bleeding tendency, and therapeutic concept that FVIII should be replaced for controlling bleeding episodes or for prophylaxis. Consequently, intrinsic or extrinsic ethnic factors are unlikely to have a marked impact on the efficacy and safety of lonoctocog alfa. Concerning the efficacy of lonoctocog alfa, therefore, PMDA decided to evaluate the inhibitory effect of routine prophylaxis treatment on bleeding tendency and the hemostatic efficacy of on-demand treatment in controlling bleeding, based mainly on the results from Study 1001, a global study, as well as those from Study 3002 in pediatric patients aged <12 years. Concerning safety, PMDA decided to evaluate the incidence and severity of adverse events and the status of inhibitor formation based on the evaluation data from Studies 1001 and 3002. PMDA also decided to examine data of the incidence and severity of adverse events from Study 3001, an ongoing continuous treatment study to Studies 1001 and 3002 being conducted by the applicant, although this study is not included in the application data package submitted (Table 14).

7.R.2 Efficacy

7.R.2.1 Efficacy of on-demand treatment

The proportion of bleeding episodes for which hemostatic efficacy was rated as “excellent” or “good” was 92.3% (783 of 848 episodes) in Study 1001 in patients aged ≥12 and ≤65 years. The

corresponding proportion in Study 3002 in patients aged <12 years was 96.3% (334 of 347 episodes), showing a similar efficacy to that in patients aged ≥12 years. The proportion of bleeding episodes for which hemostasis was achieved by 1 or 2 doses of lonoctocog alfa, a secondary endpoint, was 93.5% (793 of 848 episodes) in Study 1001 and 95.7% (332 of 347 episodes) in Study 3002.

Given that lonoctocog alfa demonstrated high hemostatic efficacy in both studies, PMDA concluded that efficacy of on-demand treatment with lonoctocog alfa can be expected in patients including children.

7.R.2.2 Efficacy of perioperative management

In Study 1001, the hemostatic efficacy of lonoctocog alfa used for perioperative management was rated based on a 4-grade rating scale. The hemostatic efficacy was found to be either "excellent" or "good" in all the 16 surgical procedures evaluated.

Considering that the replacement of FVIII is essential for patients with FVIII deficiency undergoing surgery and that the hemostatic efficacy of lonoctocog alfa was demonstrated in clinical studies, PMDA concluded that efficacy of lonoctocog alfa can be expected in perioperative management of bleeding in patients including children.

7.R.2.3 Efficacy of routine prophylaxis

The applicant explained the reason for comparing the on-demand group and the prophylaxis group in Parts 2 and 3 of Study 1001, which was not designed as a randomized study, as follows:
Given that routine prophylaxis with FVIII products has been implemented as a standard therapy for patients with severe hemophilia A in many of the participating countries in Study 1001, it was considered ethically inappropriate to randomize some of the patients receiving routine prophylaxis to the on-demand group, which could have increased the risk of bleeding in these patients. Therefore, all subjects who had received routine prophylaxis before enrollment in Study 1001 were assigned to the prophylaxis group in Parts 2 and 3. In Part 2, all subjects who had received on-demand treatment before enrollment in Study 1001 were assigned to the on-demand group.

While a difference in subject characteristics could not be ruled out between those assigned to the prophylaxis group and those assigned to the on-demand group, subgroup analyses were performed using a history of treatment with FVIII products (on-demand or routine prophylaxis) and the presence or absence of target joints as baseline characteristics, taking account of potential effects of subject characteristics on efficacy evaluation. The results of the subgroup analyses shown in Table 21 are consistent with the overall results of the study (Table 17), indicating that the between-group difference in subject characteristics has no impact on the efficacy conclusion. The AsBR in the prophylaxis group of Study 1001 was comparable to the corresponding results of existing FVIII products reported

(median, 0.0-4.1/person-year, *Haemophilia.* 2004;10:428-37; *Blood.* 2014;123:317-25, etc.); therefore, efficacy of lonoctocog alfa can be expected when used for routine prophylaxis.

Table 21. Subgroup analyses of AsBR in Study 1001 (Efficacy analysis set)

Subject characteristics		On-demand (27 subjects)		Prophylaxis (146 subjects)	
		Number of subjects	Median [range]	Number of subjects	Median [range]
History of treatment with FVIII products[a]	On-demand treatment	26	13.0 [0, 151.0]	61	0.0 [0, 40.6]
	Routine prophylaxis	0	–	82	0.0 [0, 16.0]
Target joint[b]	Present	15	26.7 [8.3, 151.0]	13	12.3 [2.6, 40.6]
	Absent	12	2.8 [0, 28.7]	133	0.0 [0, 9.1]

a Excluding subjects who had received both on-demand treatment and routine prophylaxis in the history of their treatment with FVIII products

b Defined as chronic hemarthrosis in at least 1 large joint (ankle, knee, or elbow joint) or at least 3 spontaneous bleeding episodes occurring in the same joint during a 6-month period

PMDA's view:

PMDA considers the following explanation of the applicant acceptable: Study 1001 was designed as a non-randomized study because it would have been inappropriate to randomize subjects who had received routine prophylaxis before study enrollment to the on-demand group, taking into account the status of routine prophylaxis with FVIII products for patients with severe hemophilia A in participating countries of Study 1001. In Japan, it has been reported that 60.3% (1669 of 2767) of patients with hemophilia A are receiving routine prophylaxis with FVIII products (Fiscal 2016 Report of National Survey on Coagulopathy, a project sponsored by the Ministry of Health, Labour and Welfare). Nine of the 10 Japanese subjects participating in Study 1001 had received routine prophylaxis before study enrollment and were assigned to the prophylaxis group.

As the applicant explained, a comparison between the prophylaxis group and the on-demand group in Study 1001 seems to have limitations. Nevertheless, while some baseline characteristics showed a difference between the groups in Study 1001, a statistically significant difference was observed in AsBR between the on-demand group and the prophylaxis group in Parts 2 and 3 (Table 17) and the results of subgroup analyses were consistent with the overall results of the study (Table 21). Based on the results of a comparison with other FVIII products, by using information obtained from the literature, the efficacy of lonoctocog alfa in routine prophylaxis is considered comparable to that of existing FVIII products. The median AsBR in the prophylaxis group of Study 3002 in children aged <12 years was 0.00/person-year, which was as low as that in Study 1001. Based on the above, PMDA concluded that efficacy of lonoctocog alfa can be expected in use for routine prophylaxis in children as well.

7.R.2.4 Consistency of results between overall patients and Japanese patients

PMDA views the consistency of efficacy between the overall patient population and the Japanese patient population as follows:

The results of efficacy evaluation (on-demand treatment and routine prophylaxis) in overall subjects and Japanese subjects in Study 1001 are shown in Table 22. Although the number of Japanese subjects was extremely limited, the results of evaluation of any endpoint were similar between the overall subjects and Japanese subjects. Therefore, PMDA concluded that efficacy of lonoctocog alfa can be expected in Japanese patients also.

Table 22. Results of efficacy in Study 1001 (Efficacy analysis set)

Efficacy endpoint	Japanese subjects		Overall subjects	
	On-demand (1 subject)	Prophylaxis (9 subjects)	On-demand (27 subjects)	Prophylaxis (146 subjects)
Proportion of bleeding episodes for which hemostatic efficacy was rated as "excellent" or "good"	89.7% (26 of 29 episodes)		92.3% (783 of 848 episodes)	
Proportion of bleeding episodes for which hemostasis was achieved by 1 or 2 doses of lonoctocog alfa	82.8% (24 of 29 episodes)		93.5% (793 of 848 episodes)	
Median AsBR [range] (/person-year)	3.55	0.00 [0.0, 13.0]	11.73 [0.0, 151.0]	0.00 [0.0, 40.6]

7.R.3 Safety

7.R.3.1 Safety of lonoctocog alfa

In Studies 1001 and 3002, 185 of 258 subjects receiving lonoctocog alfa achieved at least 50 exposure days. As serious adverse events, 9 events (1 event each of tonsillar haemorrhage, anaemia, thrombocytopenia, hypersensitivity, blood uric acid increased, varices oesophageal, viral infection, ankle fracture, and suicidal ideation) occurred in 7 subjects in Study 1001, and 11 events (3 events of anaemia and 1 event each of laceration, device occlusion, dyspepsia, bacteraemia, pneumonia, systemic inflammatory response syndrome, hand fracture, and splenic rupture) occurred in 9 subjects in Study 3002. All these serious adverse events, excluding 1 event of hypersensitivity in 1 subject (outcome assessed as resolved) in Study 1001, were assessed as not related to the study drug, and their outcomes were assessed as resolved.

The applicant explained the safety of lonoctocog alfa in children as follows:

The incidence of adverse events in Study 3002 in subjects aged <12 years was 76.2% (64 of 84 subjects), which was higher than that in Study 1001 in subjects aged ≥12 and ≤65 years, 64.9% (113 of 174 subjects). The adverse events that occurred with a higher incidence in subjects aged <12 years than in subjects aged ≥12 years were pyrexia, infection, and injury-related events. One event of hypersensitivity was the only adverse event that occurred in a subject aged <12 years for which a causal relationship with the study drug could not be ruled out. However, this event was mild and non-serious and resolved within the day of onset. Also in ongoing Study 3001, no adverse events that could be of new clinical concern occurred in any subjects including children by the data cut-off date ([redacted], 20[redacted]). Considering no marked difference in the safety profile of lonoctocog alfa between subjects aged ≥12 years and those aged <12 years, lonoctocog alfa also seems to be well tolerated in subjects aged <12 years.

Taking into account that the submitted data from clinical studies show no difference in the safety profile of lonoctocog alfa between subjects aged <12 years and those aged ≥12 years, PMDA concluded that lonoctocog alfa is tolerable in patients including children.

7.R.3.2 Inhibitor formation, shock, and anaphylaxis

PMDA discussed FVIII inhibitors, shock, and anaphylaxis, adverse events reported in existing FVIII products, as follows.

7.R.3.2.1 FVIII inhibitors

The applicant provided the following explanation of FVIII inhibitor formation:

No subjects developed FVIII inhibitors in Study 1001 or 3002. In ongoing Study 3001, which was initially performed as a continuous treatment study to Studies 1001 and 3002, changes made to the protocol during the study enabled hemophilia A patients without a history of treatment with FVIII products to be also regarded as eligible for study participation. By the data cut-off date ([redacted], 20[redacted]) for Study 3001, inhibitor formation did not occur in subjects who were previously treated with FVIII products and occurred in 2 hemophilia A subjects who were not previously treated with FVIII products. As of [redacted], 20[redacted], when safety information obtained later than the data cut-off date was also available, inhibitor formation occurred in 5 of 12 subjects enrolled in Study 3001 who were not previously treated with FVIII products. The lonoctocog alfa exposure days in these 5 subjects were 8, 13, 17, 20, and 32 days, respectively, when they developed FVIII inhibitors. All these subjects, excluding 1 subject withdrawn from the study after experiencing inhibitor formation when achieving 8 exposure days to lonoctocog alfa, are continuing the study treatment.

It has been reported that inhibitor formation occurred in approximately 30% of hemophilia A patients without a history of treatment with FVIII products (*Blood.* 2014;124:3389-97). At present, Study 3001 has enrolled as few as 12 hemophilia A patients without a history of treatment with FVIII products; therefore, it is considered difficult to make any conclusive statement about the incidence of formation of inhibitors against lonoctocog alfa.

7.R.3.2.2 Shock and/or anaphylaxis

The applicant explained shock and anaphylaxis as follows:

In clinical studies of lonoctocog alfa, hypersensitivity-related adverse events, such as rash, occurred in 15 subjects (20 events) in Study 1001, 13 subjects (19 events) in Study 3002, and 1 subject (3 events) in Study 3001 up to the data cut-off date ([redacted], 20[redacted]), while no subjects experienced shock or anaphylaxis. Nevertheless, the possibility that lonoctocog alfa, similarly to existing FVIII products, may cause shock or anaphylaxis cannot be ruled out. Therefore, precautions for this risk will be included in the package insert, as in the package inserts of existing FVIII products.

PMDA's view:

It is appropriate to include precautions regarding the potential risk of inhibitor formation, shock, and anaphylaxis in the package insert or other relevant documents. Taking into account that patients with hemophilia A may develop anaphylaxis or allergic reactions when treated with existing FVIII products, though less frequently compared to patients with hemophilia B (*Blood Coagul Fibrinolysis.* 2009;20:225-9), and that the neutralizing action of inhibitors may affect the efficacy of lonoctocog alfa, information on inhibitor formation is of major significance. Therefore, any newly obtained information from the ongoing study or in the post-marketing settings should be adequately provided to those involved in routine clinical practice in a prompt manner.

7.R.4 Indication

Based on the results from clinical studies in patients with hemophilia A with <1% FVIII activity receiving on-demand treatment, perioperative management, or routine prophylaxis, PMDA concluded that efficacy of lonoctocog alfa can be expected and that its clinical positioning is comparable to that of existing FVIII products. Consequently, PMDA concluded that the indication of lonoctocog alfa should be "control of bleeding tendency in patients with blood coagulation factor VIII deficiency," similarly to that of existing FVIII products.

7.R.5 Dosage and administration

7.R.5.1 Dosage and administration for on-demand treatment

The applicant explained the proposed dosage and administration for on-demand treatment as follows:

In Studies 1001 and 3002, lonoctocog alfa should be administered for treatment of a bleeding episode at a dose needed for hemostasis, which was calculated in accordance with the recommendation in the WFH Guidelines. Based on the above, the following dosage and administration was proposed: "The dose for on-demand treatment of bleeding should be calculated based on the patient's body weight and the required blood coagulation factor VIII activity level in circulating plasma." The median [range] dose for treating a bleeding episode was 31.7 [6, 84] IU/kg in Study 1001 and 27.3 [16, 76] IU/kg in Study 3002.

PMDA's view:

The median dose for treating a bleeding episode was approximately 30 IU/kg in both studies. Taking into account the above as well as the dosage and administration statements for existing recombinant FVIII products, PMDA concluded that the dosage and administration statement for lonoctocog alfa for on-demand treatment should be as follows: the usual dose is 10 to 30 IU/kg; the dose may be adjusted according to the patient's condition. Considering that information on the efficacy and safety of lonoctocog alfa administered for perioperative management of bleeding was also obtained from clinical studies, lonoctocog alfa may be administered not only for on-demand treatment but also for perioperative management.

7.R.5.2 Dosage and administration for routine prophylaxis

The applicant explained the proposed dosage and administration for routine prophylaxis as follows:

As the recommended starting dose and regimen for routine prophylaxis, lonoctocog alfa was administered at 20 to 40 IU/kg every other day or 20 to 50 IU/kg 2 or 3 times weekly in Study 1001 and at 15 to 50 IU/kg every other day or 2 or 3 times weekly in Study 3002. It was permissible for the subsequent doses to be adjusted according to each patient's condition. Considering that clinical response in children may be different from that in adults, 15 IU/kg was chosen as the lower limit of the starting dose in Study 3002, unlike in Study 1001. However, both in Study 1001 and Study 3002, lonoctocog alfa was administered within a dose range from approximately 20 to 50 IU/kg to children and adults from the start day to the end day of study treatment. The proportion of subjects who received treatment every other day was 6.4% (9 of 141 subjects) in Study 1001 and 4.1% (3 of 74 subjects) in Study 3002 at the end of each study, indicating that most subjects received study treatment 2 or 3 times weekly. The above results suggested that the appropriate starting dose and regimen are 20 to 50 IU/kg administered 2 or 3 times weekly. In clinical studies, subsequent doses after initiation of treatment with lonoctocog alfa could be adjusted to be even outside the range of 20 to 50 IU/kg according to each subject's condition. Actually, a small number of subjects (1 in Study 1001 and 7 in Study 3002) received the study drug at ≥50 IU/kg. Taking the above into account, the following dosage and administration statement for routine prophylaxis was proposed: "The usual starting dose for routine prophylaxis is 20 to 50 IU per kg (body weight) administered 2 or 3 times weekly. The dosage regimen may be adjusted according to the patient's condition."

PMDA's view:

The proposed dosage and administration, "20 to 50 IU per kg (body weight) administered 2 or 3 times weekly," is within a range specified in clinical studies, and most subjects were treated in accordance with this range of dosage and administration, based on which the efficacy and safety of lonoctocog alfa were confirmed. Therefore, the dosage and administration should be as follows without making a distinction between the starting dose and subsequent doses: "The usual dosage is 20 to 50 IU per kg (body weight) administered 2 or 3 times weekly."

Based on the results of the review presented in Section "7.R.5.1 Dosage and administration for on-demand treatment" and "7.R.5.2 Dosage and administration for routine prophylaxis," PMDA concluded that the dosage and administration statement for lonoctocog alfa should be as follows:

Dosage and Administration

The product is reconstituted with the entire vial of the solvent supplied and is slowly injected intravenously.

The usual dosage is 10 to 30 International Units (IU) per kg (body weight). The dose may be adjusted according to the patient's condition.

The usual dosage for routine prophylaxis is 20 to 50 IU per kg (body weight) administered 2 or 3 times weekly.

7.R.6 Post-marketing investigations

The applicant explained the post-marketing surveillance for lonoctocog alfa as follows:

In order to confirm the safety and efficacy of lonoctocog alfa in routine clinical use, a use results survey will be conducted in patients with blood coagulation factor VIII deficiency (target sample size of 40; observation period of 2 years). The target sample size was selected taking account of the number of patients to be treated with the drug as estimated by market research in Japan as well as feasibility. The survey period will be 6 years. Incidence of adverse events including inhibitor development, shock, and anaphylaxis will be collected in the survey.

PMDA's view:

Since clinical experience with lonoctocog alfa in Japanese clinical settings is restricted due to the very limited number of Japanese patients who participated in the clinical studies of lonoctocog alfa, the applicant should conduct post-marketing surveillance of lonoctocog alfa in routine clinical settings. It is important to conduct an evaluation of safety information collected via post-marketing surveillance, including a comparative evaluation with safety information from the submitted clinical study data, to determine the necessity for further surveillance.

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

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

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

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

The new drug application data (CTD 5.3.5.1-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. PMDA acknowledged overall GCP compliance in the conduct of clinical studies and concluded that there were no obstacles to conducting its review based on the application documents submitted. The following issues were identified at some study sites, and the heads of the relevant study

sites were notified of these issues as findings requiring improvement. However, the issues did not significantly affect the outcome of the overall assessment of the studies.

Findings requiring improvement

Study sites

- A fault in study drug management (provision of expired study drug to some subjects)
- Informed consent forms were not dated or signed by legal representatives of participants, although their consent to study participation was confirmed.

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

Based on the submitted data, PMDA has concluded that the efficacy of lonoctocog alfa in controlling bleeding tendency in patients with blood coagulation factor VIII deficiency can be expected, and that its safety is acceptable in view of its observed benefits. PMDA considers that lonoctocog alfa is clinically significant as a treatment option for controlling bleeding tendency in patients with blood coagulation factor VIII deficiency.

PMDA has concluded that lonoctocog alfa may be approved when efficacy, safety, post-marketing surveillance, etc., are further reviewed in the Expert Discussion and lonoctocog alfa is considered to have no particular problems.

Review Report (2)

August 7, 2017

Product Submitted for Approval

Brand Name	Afstyla I.V. Injection 250
	Afstyla I.V. Injection 500
	Afstyla I.V. Injection 1000
	Afstyla I.V. Injection 1500
	Afstyla I.V. Injection 2000
	Afstyla I.V. Injection 2500
	Afstyla I.V. Injection 3000
Non-proprietary Name	Lonoctocog Alfa (Genetical Recombination)
Applicant	CSL Behring K.K.
Date of Application	October 27, 2016

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 in the following. 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 conclusion on issues presented in Sections "7.R.2 Efficacy," "7.R.3 Safety," "7.R.4 Indication," and "7.R.5 Dosage and administration" in the Review Report (1).

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

1.1 Risk management plan (draft)

The expert advisors supported PMDA's conclusion on the issues presented in Section "7.R.6 Post-marketing investigations" in the Review Report (1). In addition, the following comments were made by the expert advisors:

- Because of limited experience in the use of lonoctocog alfa in children aged <12 years (including perioperative use), post-marketing data collection is important.
- The development of inhibitors was identified in several subjects in a clinical study on lonoctocog alfa [see Section "7.R.3.2.1 FVIII inhibitors" in the Review Report (1)]. Until now, treatment

experience with lonoctocog alfa has been extremely limited in patients with a history of treatment with existing blood coagulation factor VIII (hereinafter referred to as FVIII) products. This precludes comparison of the frequency of inhibitor development following treatment with lonoctocog alfa with that following treatment with the existing FVIII products. While lonoctocog alfa is considered to have acceptable safety based on currently available information, further information on the development of inhibitors should be collected in the post-marketing setting as done for the existing FVIII products.

- One-stage clotting assay may underestimate FVIII activity of lonoctocog alfa. Healthcare professionals should be advised that measured values from a one-stage clotting assay be corrected for use to monitor plasma FVIII activity following treatment with lonoctocog alfa [see Section "6.1.2 Results of synthetic substrate assay and one-stage clotting assay" in the Review Report (1)] through written materials.

In view of the expert advisors' comments above, PMDA has concluded that the risk management plan (draft) for lonoctocog alfa should include the safety and efficacy specifications presented in Table 23, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 24 and Table 25. The applicant responded that the risk management plan (draft) would be appropriately implemented.

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

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Expression of inhibitors	• Shock, anaphylaxis • Dosage error attribuatble to FVIII activity assay	Not applicable
Efficacy specification		
• Efficacy in routine clinical practice		

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

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Use-results survey • Post-marketing clinical study (continuous treatment study)[a]	• Early post-marketing phase vigilance • Preparation and distribution of materials for healthcare professionals

a The ongoing Study CSL627_3001 will be reclassified as a post-marketing clinical study after approval of lonoctocog alfa and will be continued until the product becomes available at medical institutions.

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

Objective	To confirm the safety and efficacy of lonoctocog alfa in routine clinical practice (including long-term use)
Survey method	Central registration method
Population	Patients with FVIII deficiency
Observation period	2 years
Planned sample size	40 patients
Main survey items	Patient characteristics, details of of lonoctocog alfa treatment (including information on surgery if used in perioperative management), concomitant medications and therapies, laboratory tests (including FVIII activity monitoring and FVIII inhibitor measurements), adverse events, efficacy

2. 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. The product is classified as a drug with a new active ingredient, thus 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. 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 is reconstituted with the entire vial of the solvent supplied and is slowly injected intravenously.

The usual dosage is 10 to 30 International Units (IU) per kg (body weight). The dose may be adjusted according to the patient's condition.

The usual dosage for routine prophylaxis is 20 to 50 IU per kg (body weight) administered 2 or 3 times weekly.

Condition of Approval

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