Report on the Deliberation Results

September 14, 2016

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

Brand Name	Idelvion I.V. Injection 250
	Idelvion I.V. Injection 500
	Idelvion I.V. Injection 1000
	Idelvion I.V. Injection 2000
Non-proprietary Name	Albutrepenonacog Alfa (Genetical Recombination) (JAN*)
Applicant	CSL Behring K.K.
Date of Application	December 17, 2015

Results of Deliberation

In the meeting held on September 9, 2016, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

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

Conditions for Approval

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

**Japanese Accepted Name (modified INN)*

Review Report

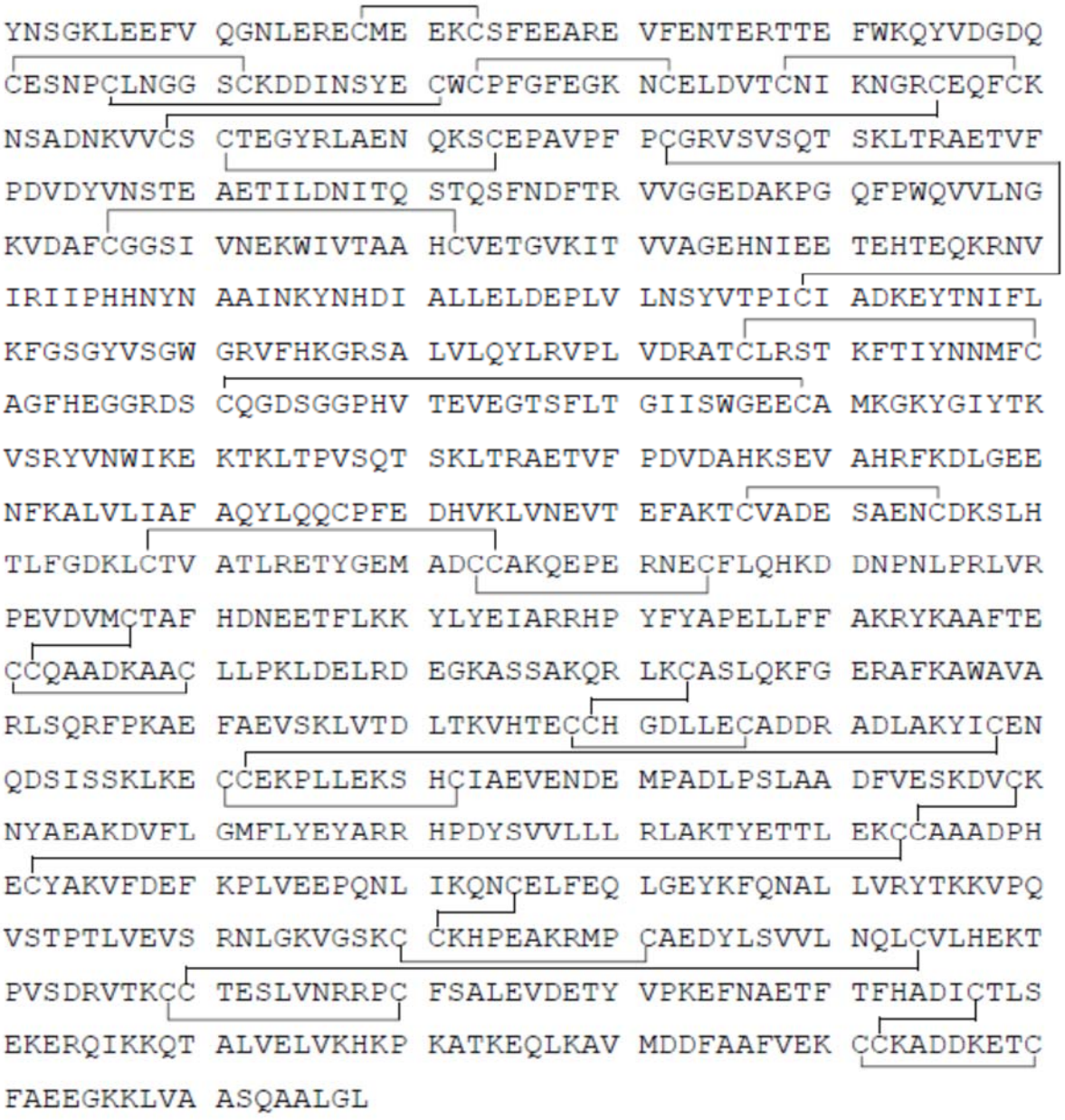
August 23, 2016
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Idelvion I.V. Injection 250 Idelvion I.V. Injection 500 Idelvion I.V. Injection 1000 Idelvion I.V. Injection 2000
Non-proprietary Name	Albutrepenonacog Alfa (Genetical Recombination)
Applicant	CSL Behring K.K.
Date of Application	December 17, 2015
Dosage Form/Strength	Lyophilized powder to be reconstituted prior to intravenous injection: Each vial contains 250, 500, 1000, or 2000 international units (IU) of Albutrepenonacog Alfa (Genetical Recombination).
Application Classification	Prescription drug, (1) Drug containing a new active ingredient
Definition	Albutrepenonacog alfa is a recombinant fusion glycoprotein whose amino acid sequences at positions 1-415 and 434-1,018 correspond to human blood coagulation factor IX and human albumin, respectively. Albutrepenonacog alfa is produced in Chinese hamster ovary cells, which is a glycoprotein (molecular weight: ca. 125,000) consisting of 1,018 amino acid residues.

Structure

Amino acid sequence and disulfide bonds:



Partial γ-carboxylation: E7, E8, E15, E17, E20, E21, E26, E27, E30, E33, E36, E40

Partial β-hydroxylation: D64

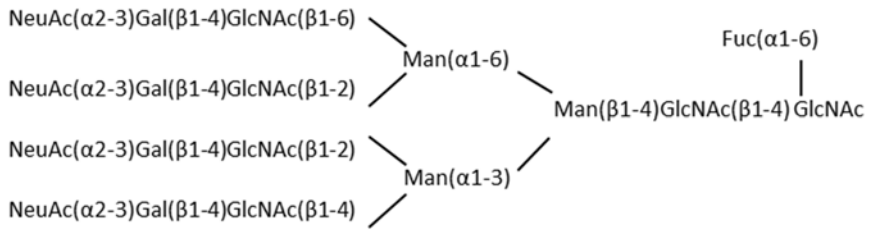
Partial sulfation: Y155

Partial phosphorylation: S158

Glycosylation: S53, S61, N157, T159, N167, T169, T172, T179

Putative structures of main carbohydrate chains

N157, N167



S53

Xyl-Xyl-Glc

S61

Fuc

GlcNAc-Fuc

Gal-GlcNAc-Fuc

NeuAc-Gal-GalNAc-Fuc

T148, T159, T163, T169 or T172; T179

$NeuAc_{1,2}$ { Gal-GalNAc

Molecular formula: $C_{5077}N_{7846}O_{1588}PS_{67}$ (protein part) (with γ-carboxylation of E7, E8, E15, E17, E20, E21, E26, E27, E30, E33, E36, and E40; β-hydroxylation of D64; sulfation of Y155; and phosphorylation of S158)

Molecular weight: approximately 125,000

Items Warranting Special Mention None

Reviewing office Office of Vaccines and Blood Products

Results of Review

As shown in the Attachment, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of the product in controlling bleeding tendency in patients with blood coagulation factor IX deficiency has been demonstrated by the submitted data and that its safety is acceptable in view of its observed benefits.

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. However, PMDA considers that its safety in routine clinical practice should be investigated in the post-marketing surveillance.

Indication

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

Dosage and Administration

Albutrepenonacog alfa should be reconstituted with the entire volume of the supplied diluent, and then injected slowly intravenously.

The usual dose is 50 IU/kg body weight, and it may be adjusted according to the patient's condition.

For routine prophylaxis, the usual dosage is 35 to 50 IU/kg body weight once every 7 days. Patients may be switched to 75 IU/kg body weight once every 14 days according to their condition. Regardless of the dosing interval, the dose should be adjusted as appropriate and must not exceed 75 IU/kg body weight.

Conditions for Approval

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

Attachment

Review Report (1)

July 13, 2016

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	Idelvion I.V. Injection 250 Idelvion I.V. Injection 500 Idelvion I.V. Injection 1000 Idelvion I.V. Injection 2000
Non-proprietary Name	Albutrepenonacog Alfa (Genetical Recombination)
Applicant	CSL Behring K.K.
Date of Application	December 17, 2015
Dosage Form/Strength	Lyophilized powder to be reconstituted prior to intravenous injection: Each vial contains 250, 500, 1000, or 2000 international units (IU) of Albutrepenonacog Alfa (Genetical Recombination) to be reconstituted prior to administration.
Proposed Indication	Control of bleeding tendency in patients with blood coagulation factor IX deficiency

Proposed Dosage and Administration

Albutrepenonacog alfa should be reconstituted with the entire volume of the supplied diluent, and then injected slowly intravenously over a few minutes.

For the treatment of acute bleeding, Albutrepenonacog alfa should be administered at the required dose calculated on the basis of the patient's body weight and the target increment of blood coagulation factor IX.

For routine prophylaxis, the recommended starting dosage of Albutrepenonacog alfa is 25 to 40 IU/kg body weight once every 7 days or 50 to 75 IU/kg body weight once every 14 days. Subsequent doses and dosing intervals should be adjusted as appropriate according to the patient's condition and clinical response, but the dose must not exceed 100 IU/kg body weight.

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List of Abbreviations

AsBR	Annualized spontaneous bleeding rate
aPTT	Activated partial thromboplastin time
AUC	Area under the concentration-time curve
$AUC_{0-\infty}$	Area under the concentration-time curve from 0 to infinity
AUC_{0-t}	Area under the concentration-time curve from 0 to the last measurable time point
CAL	Cells at the limit of *in vitro* cell age used for production
cDNA	complementary DNA
CL	Clearance
C_{max}	Maximum plasma concentration
CQA	Critical quality attributes
ELISA	Enzyme-linked immunosorbent assay
FIX	Blood coagulation factor IX
FIX KO mouse	FIX-knockout mouse
FVIIa/TF	Activated form of blood coagulation factor VII/Tissue Factor
FXIa	Activated form of blood coagulation factor XI
HCP	Host cell derived protein
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IR	Incremental recovery recorded 30 minutes after injection
IU	International units
MCB	Master cell bank
MedDRA/J	Medical Dictionary for Regulatory Activities / Japanese version
MMV	Murine minute virus
MRT	Mean retention time
PACE/Furin	Paired basic amino acid cleaving enzyme/Furin
QbD	Quality by design
RCB	Research cell bank
rIX-FP	Recombinant blood coagulation factor IX-fusion protein
rIX-FPa	Activated form of recombinant blood coagulation factor IX-fusion protein
rIX-FPα	Recombinant blood coagulation factor IX alpha-fusion protein
RP-HPLC	Reversed phase high performance liquid chromatography
SDS-PAGE	Sodium dodecyl sulfate -polyacrylamide gel electrophoresis
SE-HPLC	Size exclusion high performance liquid chromatography
TnBP	Tri-n-butyl-phosphate
$t_{1/2}$	Elimination half-life
V_{ss}	Volume of distribution at steady state
WBCT	Whole blood clotting time
WCB	Working cell bank
WFH	World Federation of Hemophilia
Study 2001	Study CSL654_2001
Study 2004	Study CSL654_2004
Study 3001	Study CSL654_3001
Study 3002	Study CSL654_3002
Study 3003	Study CSL654_3003
BeneFIX	BeneFIX Intravenous
PMDA	Pharmaceuticals and Medical Devices Agency
Adverse drug reaction	An adverse event assessed as “related” to the study drug
Albutrepenonacog alfa	Albutrepenonacog Alfa (Genetical Recombination)

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

Hemophilia B (congenital blood coagulation factor IX deficiency) is a bleeding disorder that is caused by a quantitative decrease or qualitative abnormalities in FIX (blood coagulation factor IX), and patients with hemophilia B may have serious bleeding episodes. The standard treatment for patients with hemophilia B is to administer the necessary and sufficient dose of FIX for hemostasis.

Currently, the following FIX products are approved in Japan: 2 human plasma-derived FIX products, Christmassin M I.V. (General incorporated association Japan Blood Products Organization) and Novact M (General Incorporated Foundation, Chemo-Sero-Therapeutic Research Institute [Kaketsuken]); 1 human plasma-derived FIX complex product, PPSB-HT for I.V. Injection (Nihon Pharmaceutical Co., Ltd.); 2 recombinant FIX products, BeneFIX Intravenous (Pfizer Japan Inc.) and Rixubis Intravenous (Baxalta Japan Limited); and a recombinant FIX Fc fusion protein product, Alprolix Intravenous (Biogen Japan Ltd.).

Albutrepenonacog alfa is a recombinant fusion protein linking FIX with albumin and has been developed to reduce injection frequency compared with the currently available FIX products.

In the development of albutrepenonacog alfa, a foreign phase I study (Study 2001) was conducted in patients with hemophilia B from [redacted] 20[redacted] through [redacted] 20[redacted]. A new drug application for albutrepenonacog alfa was submitted with data including those from the global phase II/III study (Study 3001) conducted in patients with hemophilia B in 10 countries including Japan from [redacted] 20[redacted] through [redacted] 20[redacted] and a foreign phase III study (Study 3002) conducted in children with hemophilia B from [redacted] 20[redacted] through [redacted] 20[redacted].

A new drug application for albutrepenonacog alfa was submitted in the U.S. in December 2014 and in Europe in March 2015, and the drug was approved in the U.S. in March 2016 and in Europe in May 2016.

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

2.1 Drug substance

2.1.1 Preparation and control of the cell substrates

The gene encoding albutrepenonacog alfa consists of the FIX cDNA jointed to the human serum albumin cDNA by a linker sequence containing cleavage sites specific to FXIa and FVIIa/TF. The FIX cDNA and the human serum albumin cDNA were isolated from a human liver cDNA library. The expression construct for albutrepenonacog alfa was generated by inserting a DNA encoding albutrepenonacog alfa and [redacted] gene into an expression vector. The obtained expression construct was then transfected into Chinese hamster ovary (CHO) cells, and a cell line highly expressing albutrepenonacog alfa was isolated from the CHO cells. The cell line was used to prepare the RCB, MCB, and WCB.

Identity and purity tests were performed on the MCB, WCB, and CAL according to the ICH Q5A (R1), Q5B, and Q5D, and the cell bank system was confirmed genetically stable during the manufacturing process. In these tests, no adventitious viruses or nonviral adventitious agents were detected for any parameters studied.

Appropriate storage conditions were established for the MCB and WCB. There is no plan to prepare a new MCB, but a new WCB will be generated as necessary.

2.1.2 Manufacturing process

The manufacturing process of the drug substance comprises the following steps: [redacted], [redacted], [redacted], [redacted], [redacted] ([redacted]), viral inactivation by [redacted], filtration and [redacted] of virus-inactivated fluid, [redacted], [redacted], [redacted], [redacted], [redacted], [redacted] ([redacted]), and virus removal filtration. The drug substance is stored in an ethylene-vinyl acetate copolymer bag at ≤−65°C.

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

The filtrate after [redacted] virus inactivation is defined as the intermediate of the drug substance, and the specifications, storage temperature, and storage duration are controlled appropriately. The manufacturing process for the drug substance was validated in a commercial scale.

2.1.3 Safety evaluation of adventitious agents

No raw materials of animal origin were used in the manufacturing process of the drug substance, except for CHO cells used as the host cell, which are confirmed to meet the Standards for Biological Ingredients.

The MCB, WCB, and CAL were subjected to purity tests and no adventitious viruses or nonviral adventitious agents were detected.

[redacted] ([redacted]) were subjected to sterility testing, mycoplasma testing, adventitious virus testing (*in vitro* test), [redacted], and [redacted], and no adventitious viruses or non-viral adventitious agents were detected.

As shown in Table 1, the manufacturing process was subjected to viral clearance tests with model viruses and the capacity of the purification process to remove viruses to a certain level has been demonstrated. The lowest value measured by multiple independent tests ([redacted] test for the [redacted] step) was used as the virus reduction factor for each step.

Table 1. Results of viral clearance tests

Manufacturing process	Virus reduction factor (log_{10})			
	Murine leukemia virus MuLV	Bovine viral diarrhea virus BVDV	Pseudorabies virus PRV	Canine parvovirus CPV
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Virus removal filtration	[redacted]	[redacted]	[redacted]	[redacted]
Overall reduction factor [a)]	≥17.2 (≥13.0)	≥14.5 (≥10.8)	≥21.2 (≥12.6)	≥7.5 (≥6.1)

[a)] The values in the parenthesis represent overall reduction factor which do not include the reduction factor for the [redacted] step because the test in this step using reused resin was not performed more than once under the same conditions.

2.1.4 Manufacturing Process Development

The major changes made in the manufacturing process during the development of the drug substance are shown in Table 2. The 4 manufacturing processes (Manufacturing Processes A, B, C, and D [the proposed manufacturing process]) were successively developed. The drug product from a drug substance manufactured by Manufacturing Process B was used in the phase I and I/II studies, and the drug product from drug substances manufactured by Manufacturing Processes C and D was used in the phase III studies [see Sections 7.1, 7.2, and 7.3]. The comparability of quality attributes has been established between the drug substances before and after the changes made in the manufacturing process.

A QbD approach has been applied to develop the manufacturing process [see Section 2.3].

Table 2. Major changes made in manufacturing process specifications

	Changes
Between Manufacturing Process A and B	・ ・ ・ ・ [redacted]
Between Manufacturing Processes B and C	・ ・ ・ ・ ・ [redacted]
Between Manufacturing Processes C and D	・ ・ ・ [redacted]

2.1.5 Characterization

2.1.5.1 Structure and physicochemical and biological properties

Characterization was conducted as shown in Table 3.

Table 3. Outline of characterization

Attributes	Properties	Study methods
Structure	Primary structure and disulfide bonds	[redacted]
	Secondary and higher-order structures	
	Aggregates and truncated forms	SE-HPLC
	Post-translational modification (amino acid modification)	[redacted]
	Carbohydrate structure	
Physiochemical properties	Molar absorptivity	
	Specific activity	
Biological properties	Interaction with neonatal Fc receptor	
	Interaction with the activated form of blood coagulation factor VIII	
	Tenase complex formation	[redacted]
	Activation of FX by rIX-FPa	
	Structural change in rIX-FP by FXIa	SDS-PAGE
	Structural changes in rIX-FP by TF, FVIIa, and/or phospholipid	SDS-PAGE
	Thrombin generation potential by activation of rIX-FP via endogenous and exogenous pathways	[redacted]
	Inhibition of rIX-FPa activity by antithrombin III and/or heparin	

2.1.5.2 Product-related substances and product-related impurities

On the basis of the above analysis results and other data, the aggregates including dimers, the truncated form (rIX-FPα), and the activated form (rIX-FPa) were determined to be product-related impurities and are controlled by the specifications for the drug substance and the drug product.

2.1.5.3 Process-related impurities

The process-related impurities identified include microorganisms, endotoxins, Impurity 1, Impurity 2, Impurity 3, Impurity 4, Impurity 5, Impurity 6 (Impurities 6-1, 6-2, 6-3, and 6-4), Impurity 7, and Impurity 8. All of these process-related impurities are found to be removed sufficiently in the manufacturing process. Microorganisms, endotoxins, and Impurity 3 are controlled by the specifications for the drug substance, and Impurities 1 and 2 and endotoxins are controlled by the specifications for the drug product.

2.1.6 Control of drug substance

The specifications for the drug substance include description, identification ([redacted] and peptide mapping), [redacted], purity (SE-HPLC for Product-related Impurity 1, the desired product, and Product-related Impurity 2; RP-HPLC for [redacted]), [redacted], endotoxins, microbial limits, potency, and [redacted].

[redacted] and [redacted] were specified during the review.

2.1.7 Stability of drug substance

Main stability studies of the drug substance are shown in Table 4.

Table 4. Outline of main stability studies of the drug substance

Study	No. of batches	Storage condition	Storage period	Storage container
Long-term	3	≤−65°C	24 months	Ethylene-vinyl acetate copolymer bag
Accelerated	3	−15°C	12 months	
Stress (temperature)	1	40°C ± 2°C	4 weeks	Glass vial
Stress (light)	1	25°C, 75% RH	Overall illumination of ≥1.2 million lux・h and an integrated near ultraviolet energy of ≥200 W・h/m^2	

The drug substance had not changed over entire test period when stored at −65°C in the long-term study and at −15°C in the accelerated study and has been proven to meet the required specifications. Stress study (temperature and light) showed, as measured by SE-HPLC, a decrease in the FIX activity, a decrease in the amount of the desired product and an increase in Product-related Impurity 1, suggesting that the drug substance is unstable.

On the above basis, a shelf-life of 24 months was established for the drug substance when stored at ≤−65°C in an ethylene-vinyl acetate copolymer bag.

2.2 Drug product

2.2.1 Description and composition of the drug product and formulation development

The drug product is a lyophilized powder to be reconstituted prior to injection containing 250, 500, 1000, and 2000 IU of the active ingredient in 1 vial. The drug product contains as excipients, sodium citrate hydrate (a buffer), D-mannitol (a vehicle), purified sucrose and polysorbate 80 (stabilizers), and hydrochloric acid (a pH regulator). The primary container is composed of a glass vial (6 or 10 mL) and bromobutyl rubber stopper, and the secondary package is a carton.

The drug product is supplied with reconstitution diluent, 2.5 or 5 mL of water for injection (Japanese Pharmacopoeia) in a glass vial.

2.2.2 Manufacturing process

The manufacturing process of the drug product comprises preparation and sterile filtration of the product bulk solution, filling, lyophilization, stoppering and cap sealing, labeling and packaging, and storage and testing. The preparation of the product bulk solution, [redacted], [redacted], [redacted], [redacted], and [redacted] are specified as critical steps. The manufacturing process was validated at the commercial scale.

2.2.3 Manufacturing Process Development

During the development of the drug product, the manufacturing site was changed, and the manufacturing scale was expanded. The comparability of quality attributes of the drug product before and after these changes has been established.

The drug product manufactured by the pre-change process was used in the phase I and I/II studies, and the drug product manufactured by the post-change process was used in the phase III studies [see Sections 7.1, 7.2, and 7.3].

A QbD approach has been applied to develop the manufacturing process [see Section 2.3].

2.2.4 Control of drug product

The specifications for the drug product include content, description, identification ([redacted] and SDS-PAGE), [redacted], [redacted], purity ([redacted]; SE-HPLC for Product-related Impurity 1, the desired product, and Product-related Impurity 2; RP-HPLC for [redacted]), [redacted], [redacted], [redacted], [redacted], [redacted], endotoxins, uniformity of dosage units, foreign insoluble matters, insoluble particulate matters, sterility, [redacted], [redacted], and potency.

2.2.5 Stability of drug product

The main stability studies of the drug product are outlined in Table 5.

Table 5. Outline of main stability studies of the drug product

Study	No. of batches	Storage condition	Storage period	Storage container
Long-term	250 IU: 3 500 IU: 3 1000 IU: 3 2000 IU: 3	5°C ± 3°C, 60% ± 5% RH	36 months	A bromobutyl rubber stopper and a glass vial
		25°C ± 2°C, 60% ± 5% RH		
Accelerated		40°C ± 2°C, 75% ± 5% RH	6 months	
Stress (temperature)	250 IU: 1 500 IU: 1	50°C ± 2°C	4 weeks	
Post-reconstitution stability	250 IU: 6 500 IU: 6 1000 IU: 6 2000 IU: 6	20°C to 25°C	8 hours after reconstitution	
Stress (light)	250 IU: 1 500 IU: 1	25°C, 75% RH	Overall illumination of ≥1.2 million lux･h and an integrated near ultraviolet energy of ≥200 W･h/m^2	A bromobutyl rubber stopper and a glass vial (with or without a carton)

The drug product had not changed over entire study period when stored at 5°C ± 3°C and 25°C ± 2°C in the long-term study and has been proven to meet the required specifications. A decrease in the FIX activity, a decrease in the amount of the desired product and an increase in Product-related Impurity 1 as measured by SE-HPLC were observed in the accelerated study, stored at 40°C ± 2°C, in the stress study (temperature), stored at 50°C ± 2°C, and in the photostability study. This suggests that the drug product is unstable to

temperature and light. Post-reconstitution stability was studied after reconstitution with the supplied diluent and showed that the reconstituted product was stable for 8 hours at room temperature.

On the basis of the above studies, a shelf-life of 36 months was established for the drug product when stored at 2°C to 25°C in a glass vial and protected from light and freezing.

2.3 QbD

A QbD approach was applied to develop the drug substance and the drug product, and the quality control strategy has been established. The following CQAs were identified among the quality attributes including the product-related substances, product-related impurities, and process-related impurities, and the quality attributes of the product are controlled by combination of process parameters, in-process control, and specifications.

・Identification of CQAs for the drug substance

[redacted], [redacted], [redacted], [redacted] ([redacted]), [redacted] ([redacted]), [redacted] ([redacted]), [redacted] (SDS-PAGE and [redacted]), [redacted] and size variants (SE-HPLC for Product-related Impurity 1, the desired product, and Product-related Impurity 2; RP-HPLC for [redacted]; [redacted]; and [redacted]), process-related impurities (Impurity 3, endotoxins, and microorganisms), and viral removal.

・Identification of CQAs for the drug product

[redacted], [redacted], [redacted], [redacted] ([redacted]), [redacted] (SDS-PAGE and [redacted]), [redacted] and size variants (SE-HPLC for Product-related Impurity 1, the desired product, and Product-related Impurity 2; RP-HPLC for [redacted]; [redacted]; and [redacted]), [redacted] (endotoxins), viral removal, sterility, excipients ([redacted], [redacted], [redacted], [redacted]), [redacted], [redacted], [redacted], and [redacted].

2.R Outline of the review conducted by PMDA

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

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

The applicant submitted the data from primary pharmacodynamic studies (an *in vitro* study on plasma coagulation time and *in vivo* studies in hemophilia B dogs and in FIX KO mice, an animal model of hemophilia B [*Blood.* 1997;90:3962-3966]), and the data from safety pharmacology studies in rats and cynomolgus monkeys. In these studies, BeneFIX, a recombinant FIX product, was used as a comparator.

3.1 Primary pharmacodynamics

3.1.1 *In vitro* study (effects on aPTT) (CTD 4.2.1.1.1, Study IVX 01/09)

Albutrepenonacog alfa or BeneFIX was added to human plasma to obtain a concentration of 0, 0.5, 1.0, 1.5, or 2.0 IU/mL (2 samples for each concentration), and then the aPTT was measured to investigate the dose-response of albutrepenonacog alfa in the blood coagulation system. The mean aPTT in human plasma to which albutrepenonacog alfa was added at the respective concentrations was 40.9, 39.7, 38.4, 37.4, and 37.8 sec, and the mean aPTT in human plasma to which BeneFIX was added at the respective concentrations was 43.7, 40.5, 39.0, 38.3, and 37.1 sec. The applicant stated that these results demonstrated that aPTT in human plasma tends to decrease with increasing doses of albutrepenonacog alfa or BeneFIX.

3.1.2 *In vivo* studies

The applicant submitted the following study data as *in vivo* primary pharmacodynamic studies. The applicant claimed that the data from the following 3 studies demonstrated that albutrepenonacog alfa has a hemostatic effect comparable to that of BeneFIX.

3.1.2.1 Study of coagulation activation in hemophilia B dogs (CTD 4.2.1.1.2, Study 040200011)

A single intravenous dose of albutrepenonacog alfa or BeneFIX 100 IU/kg was administered to hemophilia B dogs (n=2-3/group of both sexes) to investigate the pharmacological effects of albutrepenonacog alfa, and blood samples were collected from 5 min post dose to Day 36 to determine aPTT and WBCT values. The results showed that aPTT was shortened from approximately 100 sec at baseline to approximately 50 sec at 5 min post dose of albutrepenonacog alfa and BeneFIX. In the BeneFIX group, the shortened aPTT was gradually prolonged from Day 1 to approximately 70 sec on Day 3 or 4, while, in the albutrepenonacog alfa group, it was maintained at approximately 50 sec up to Day 3 or 4. Subsequently, aPTT returned to approximately 80% of the baseline level on Day 7.6 in the BeneFIX group and on Day 8.8 in the albutrepenonacog alfa group. WBCT was shortened from ≥60 min at baseline to approximately 10 min at 5 min post dose in both treatment groups. The shortening effect on WBCT lasted for 6 to 7 days in both treatment groups, and returned to the baseline level 2 weeks after the administration.

The applicant explained that aPTT and WBCT returned to the baseline levels with clearance of albutrepenonacog alfa and BeneFIX from circulating blood.

3.1.2.2 Hemostatic effect in a tail-tip bleeding model (CTD 4.2.1.1.3, Study NBM 04/09)

A single intravenous dose of albutrepenonacog alfa (50, 100, 200 IU/kg), BeneFIX (50, 100, 200 IU/kg), or physiological saline as the control was administered to FIX KO mice (n=15/group of both sexes) to investigate the hemostatic effect of albutrepenonacog alfa. Tail tips were resected 15 min post dose, and time to hemostasis and total blood loss were measured up to 30 min (1800 sec) post dose. The mean time to hemostasis in mice treated with 200 IU/kg (the highest dose administered) of albutrepenonacog alfa and BeneFIX was 451 and 342 sec, respectively, and was 71% and 78% lower, respectively, than that in mice treated with physiological saline (1581 sec). The mean total blood loss in mice treated with 200 IU/kg of

albutrepenonacog alfa and BeneFIX was 106 and 102 μL, respectively, and was both approximately 80% lower than that in mice treated with physiological saline (524 μL).

3.1.2.3 Study on coagulation activation study in FIX KO mice (CTD 4.2.1.1.4, Study NBM 05/09)

A single intravenous dose of albutrepenonacog alfa (50, 100, 200 IU/kg), BeneFIX (50, 100, 200 IU/kg), or physiological saline, the control, was administered to FIX KO mice (n=14-17/group of both sexes) to investigate the effects of albutrepenonacog alfa on the blood coagulation parameter (aPTT) and blood samples were collected 15 min post dose. The mean aPTT in mice treated with 200 IU/kg (the highest dose administered) of albutrepenonacog alfa and BeneFIX was 31.4 and 31.5 sec, respectively, and was approximately 35% lower than that in mice treated with physiological saline (48.4 sec).

3.2 Safety pharmacology

The effects of albutrepenonacog alfa on the central nervous, cardiovascular, and respiratory systems are shown in Table 6. The effects on the central nervous system were evaluated in a single-dose and repeated-dose toxicity studies, and those on the cardiovascular system were evaluated in a repeated-dose toxicity study [see Sections 5.1 and 5.2].

Table 6. Summary of results of safety pharmacology studies

Items	Tested systems	Endpoints and assessment methods	Highest dose	Findings	CTD
Central nervous system	Rats	General conditions, necropsy, and histopathology	500 IU/kg single dose	No effects on the central nervous system associated with albutrepenonacog alfa administration.	4.2.3.1.1
	Cynomolgus monkeys		500 IU/kg single dose		4.2.3.1.3
	Rats		500 IU/kg 4 weeks		4.2.3.2.1
	Rats		2000 IU/kg 26 weeks		4.2.3.2.3
	Cynomolgus monkeys		500 IU/kg 4 weeks		4.2.3.2.4
Cardiovascular system	Cynomolgus monkeys	Blood pressure, heart rate, and electrocardiography	500 IU/kg 4 weeks	No effects on the cardiovascular system associated with albutrepenonacog alfa administration.	4.2.3.2.4
Respiratory system	Rats	Respiratory rate, tidal volume, and minute ventilation	500 IU/kg single dose	No effects on the respiratory system associated with albutrepenonacog alfa administration.	4.2.1.3.1

3.R Outline of the review by PMDA

On the basis of the submitted data of the primary pharmacodynamic studies, PMDA considers that albutrepenonacog alfa has FIX activity and is expected to be effective in hemostasis in the body. Based on the presented data of the safety pharmacology studies, PMDA considers that no particular safety concerns exist for albutrepenonacog alfa.

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

The applicant submitted pharmacokinetic data from studies in cynomolgus monkeys, hemophilia B dogs, and rats. The concentrations of FIX in plasma samples were determined by ELISA and were converted into mIU/mL based on the specific activity of albutrepenonacog alfa. After ^{3}H-labeled ([^{3}H]-)albutrepenonacog alfa or [^{3}H]-BeneFIX was administered, tissue radioactivity was determined by quantitative whole-body autoradiography.

4.1 Absorption

The applicant submitted the following data on absorption of albutrepenonacog alfa from studies in cynomolgus monkeys and hemophilia B dogs.

4.1.1 Single-dose studies

4.1.1.1 Single-dose study in cynomolgus monkeys (CTD 4.2.2.2.1, Study APQ0002)

A single intravenous dose of albutrepenonacog alfa (50, 100 IU/kg) or BeneFIX (50, 100 IU/kg) was administered to cynomolgus monkeys (n=1/sex/group), and plasma FIX concentrations were measured at 14 time points including baseline and the time points from 5 min to 456 hours post dose. Pharmacokinetic parameter data are shown in Table 7. The $t_{1/2}$ in the BeneFIX group could not be calculated because the plasma FIX concentrations varied irregularly after BeneFIX was administered.

Table 7. Pharmacokinetic parameters in cynomolgus monkeys (mean)

Study drug		No. of animals	C_{max} (mIU/mL)	AUC_t (mIU·h/mL)	$t_{1/2}$ (h)
Albutrepenonacog alfa	50 IU/kg	2	1030	35,700	41.9
	100 IU/kg	2	1930	72,100	42.4
BeneFIX	50 IU/kg	2	649	14,400	-
	100 IU/kg	2	1800	42,200	-

All figures represent mean values of 2 monkeys in each group.

4.1.1.2 Single-dose study in hemophilia B dogs (CTD 4.2.1.1.2, Study 040200011)

A single intravenous dose of albutrepenonacog alfa or BeneFIX 100 IU/kg was administered to hemophilia B dogs (2 males and 1 female in the albutrepenonacog alfa group and 2 females in the BeneFIX group). Plasma FIX concentrations were measured at 31 time points including baseline and the time points from 5 min to 840 hours post dose. Pharmacokinetic parameter data are shown in Table 8. The levels of CL and $t_{1/2}$ were lower and higher, respectively, in the albutrepenonacog alfa group than in the BeneFIX group. The applicant stated that the results of the study showed approximately 1.5-fold longer $t_{1/2}$ in the albutrepenonacog alfa group than in the BeneFIX group, demonstrating that albutrepenonacog alfa has a longer half-life than BeneFIX.

Table 8. Pharmacokinetic parameters in hemophilia B dogs (geometric mean [95% confidence interval])

Study drug		No. of animals	C_{max}(mIU/mL)	AUC_t (mIU·h/mL)	CL (mL/h/kg)	$t_{1/2}$ (h)
Albutrepenonacog alfa	100 IU/kg	3	1105 [729, 1541]	37,986 [29,535, 48,856]	2.63 [2.05, 3.39]	51.9 [46.8, 57.6]
BeneFIX	100 IU/kg	2	616	10,743	9.31	33.6

All values in the BeneFIX group represent geometric mean of the observed values in 2 dogs.

4.2 Distribution (CTD 4.2.2.3.1, Study CSL/01)

A single intravenous dose of [^{3}H]-albutrepenonacog alfa 3.2 mg/kg (equivalent to 221 IU/kg) or [^{3}H]-BeneFIX 5 mg/kg (equivalent to 1000 IU/kg) was administered to rats (n=1 male/group/time point). Tissue radioactivity was determined at 8 time points (from 15 min to 240 hours post dose) in the [^{3}H]-albutrepenonacog alfa group and at 4 time points (from 15 min to 24 hours post dose) in the [^{3}H]-BeneFIX group. High levels of radioactivity were detected mainly in the adrenal glands, kidneys, and epiphyseal cartilage in both [^{3}H]-albutrepenonacog alfa and [^{3}H]-BeneFIX groups. The applicant explained that the study results demonstrated that albutrepenonacog alfa and BeneFIX showed comparable tissue distribution regardless of albumin fusion.

4.3 Metabolism

In accordance with the ICH S6 (R1), metabolism was not studied since albutrepenonacog alfa is a recombinant protein and is thought to be metabolized to peptides and amino acids.

4.4 Excretion (CTD 4.2.2.3.1, Study CSL/01)

A single intravenous dose of [^{3}H]-albutrepenonacog alfa 3.2 mg/kg (equivalent to 221 IU/kg) or [^{3}H]-BeneFIX 5 mg/kg (equivalent to 1000 IU/kg) was administered to rats (8 in the [^{3}H]-albutrepenonacog alfa group and 4 in the [^{3}H]-BeneFIX group). Urine and feces were collected at time points up to 240 hours post dose in the [^{3}H]-albutrepenonacog alfa group and up to 24 hours post dose in the [^{3}H]-BeneFIX group to determine the radioactivity in urine and feces. After administration of [^{3}H]-albutrepenonacog alfa, 72.9% and 4.3% of radioactivity was recovered in urine and feces, respectively, up to 240 hours post dose, and albutrepenonacog alfa was eliminated primarily in urine. The radioactivity recovered in urine and feces up to 24 hours post dose was 39.9% and 0.92%, respectively, in the [^{3}H]-albutrepenonacog alfa group and 51.0% and 8.9%, respectively, in the [^{3}H]-BeneFIX group. The applicant explained that the comparison of data up to 24 hours post dose showed that the amount of albutrepenonacog alfa retained in the body was higher than that of BeneFIX.

4.R Outline of the review by PMDA

PMDA's view:

Although $t_{1/2}$ could not be compared between albutrepenonacog alfa and BeneFIX in the study in cynomolgus monkeys [see Section 4.1.1.1], the data from the study in hemophilia B dogs [see Section 4.1.2.2] suggest that the $t_{1/2}$ of albutrepenonacog alfa is longer than that of BeneFIX.

Also it is considered acceptable that the metabolism of albutrepenonacog alfa was not studied.

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant submitted data from single-dose toxicity studies, repeated-dose toxicity studies, a genotoxicity study, a local tolerance study, and a thrombogenicity study to evaluate toxicity of albutrepenonacog alfa.

5.1 Single-dose toxicity

5.1.1 Single-dose toxicity studies in rats (CTD 4.2.3.1.1, Study APQ0005; CTD 4.2.3.1.2, Study 8244656)

A single intravenous dose of albutrepenonacog alfa 0 (physiological saline), 75, 150, or 500 IU/kg (approximately 6.7 times the proposed clinical dose) was administered to rats (n=5/sex/group). No unscheduled deaths occurred. The rats showed no changes related to administration of albutrepenonacog alfa, except for prolonged prothrombin time attributable to the pharmacological effects of albutrepenonacog alfa in the 500 IU/kg group and high plasma potassium levels in the 150 and 500 IU/kg groups.

To compare the toxicity of albutrepenonacog alfa produced from drug substances manufactured at a pilot scale and a commercial scale, a single intravenous dose of albutrepenonacog alfa 0 (physiological saline) or 500 IU/kg produced from produced from pilot or commercial scale processes, was administered to rats (n=5/sex/group). No unscheduled deaths occurred, and no differences in the toxicity profile were observed between the products manufactured in the different scale processes.

5.1.2 Single-dose toxicity study in cynomolgus monkeys (CTD 4.2.3.1.3, Study APQ0007)

A single intravenous dose of albutrepenonacog alfa 0 (physiological saline), 75, 150, or 500 IU/kg (approximately 6.7 times the proposed clinical dose) was administered to cynomolgus monkeys (n=3/sex/group). No deaths occurred. The animals showed no changes related to administration of albutrepenonacog alfa, except for mildly elevated plasma bilirubin levels in the 150 and 500 IU/kg groups.

5.2 Repeat-dose toxicity

5.2.1 Four-week intravenous toxicity study in rats with a 2-week recovery period (CTD 4.2.3.2.1, Study APQ0009)

Albutrepenonacog alfa 0 (physiological saline), 75, 150, or 500 IU/kg/day (approximately 6.7 times the proposed clinical dose) was administered intravenously to rats for 5 days (n=5/sex/group) or 4 weeks (13/sex in the 0 and 500 IU/kg/day groups; 10/sex in the 75 and 150 IU/kg/day groups). Three rats in each sex in the 0 and 500 IU/kg/day groups underwent a 2-week washout period after 4 weeks of treatment to assess recovery. Two rats in the 500 IU/kg/day groups died on the last day of administration (Day 28). In light of the effects on changes in body weight and of histopathological examinations, deaths in these rats were considered attributable to administration procedures or an accidental cause and unrelated to administration of albutrepenonacog alfa. The rats showed no changes related to administration of albutrepenonacog alfa, except for prolonged prothrombin time attributable to the pharmacological effects of albutrepenonacog alfa in the 500 IU/kg/day group. The no-observed-adverse-effect level (NOAEL) was considered to be 500 IU/kg/day.

5.2.2 Twenty-six-week intravenous toxicity study in rats with a 4-week recovery period (CTD 4.2.3.2.3, Study APQ0021)

Albutrepenonacog alfa 0 (physiological saline), 500, or 2000 IU/kg/day (approximately 26.7 times the proposed clinical dose) was administered intravenously to rats for 5 days (n=5/sex in the 0 IU/kg/day group; n=5 male and 6 female rats in the 2000 IU/kg/day group) or 26 weeks (16/sex in the

0 IU/kg/day group; 13/sex in the 500 IU/kg/day group; 17/sex in the 2000 IU/kg/day group). Three rats in each in the 0 and 500 IU/kg/day groups and 4 rats in each sex in the 2000 IU/kg/day group underwent a 4-week washout period after 26 weeks of treatment to assess recovery. Deaths occurred in 2 rats in the 0 IU/kg/day group (Days 12 and 140), 1 rat in the 500 IU/kg/day group (Day 40), and 2 rats in the 2000 IU/kg/day group (Days 1 and 173). On the basis of the histopathological examination, deaths in 3 rats in the 500 and 2000 IU/kg/day groups were considered attributable to administration procedures or an accidental cause and unrelated to administration of albutrepenonacog alfa. The rats showed no changes related to administration of albutrepenonacog alfa, except for prolonged prothrombin time attributable to the pharmacological effects of albutrepenonacog alfa. The NOAEL was considered to be 2000 IU/kg/day.

5.2.3 Four-week intravenous toxicity study in cynomolgus monkeys (CTD 4.2.3.2.4, Study APQ0001)

Albutrepenonacog alfa 0 (physiological saline), 75, 150, or 500 IU/kg/day (approximately 6.7 times the proposed clinical dose) was administered intravenously to cynomolgus monkeys for 5 days (n=1/sex/group) or 4 weeks (n=13/sex/group). No deaths occurred. The cynomolgus monkeys showed no changes related to administration of albutrepenonacog alfa, except for prolonged aPTT attributable to the pharmacological effects of albutrepenonacog alfa in the 150 and 500 IU/kg/day groups. The NOAEL was considered to be 500 IU/kg/day.

5.3 Genotoxicity

In i*n vitro* studies, an Ames test and a chromosomal aberration assay were performed in human lymphocytes in the presence and absence of S9-mix, and both tests were negative.

5.4 Carcinogenicity

No carcinogenicity studies were conducted because both human FIX and human albumin contained in albutrepenonacog alfa are proteins of human origin.

5.5 Reproductive and developmental toxicity

Hypercoagulability state during pregnancy has been considered possibly related to pregnancy loss and placenta-mediated complications (*Br J Haematol.* 2012;157:529-542). Accordingly, the risk of reproductive toxicity cannot be assessed precisely when high doses of albutrepenonacog alfa are administered to normal animals. For this reason, no reproductive toxicity studies were conducted. In single-dose and repeated dose toxicity studies in rats and monkeys [see Sections 5.1 and 5.2], no changes in male or female reproductive organs were observed in association with albutrepenonacog alfa administration. The applicant plans to prepare a precautionary statement warning that albutrepenonacog alfa should be given to pregnant or possibly pregnant women only if the potential benefits outweigh the risks since no reproductive toxicity studies of albutrepenonacog alfa have been conducted.

5.6 Local tolerance

Local tolerance of albutrepenonacog alfa was assessed in the single-dose and repeated-dose toxicity studies in rats and monkeys [see Sections 5.1 and 5.2]. No local irritation was observed in association with albutrepenonacog alfa administration. Furthermore, the following local tolerance study was conducted in rabbits.

5.6.1 Local tolerance study in rabbits (CTD 4.2.3.6.1, Study APQ0008)

Albutrepenonacog alfa (200 IU/mL) or physiological saline was administered to rabbits (n=4 females/group) at 1.2 mL in the intravenous injection group, 1.3 mL in the intra-arterial injection group, and 0.2 mL in the perivenous injection group. For any of these routes of administration, no local irritation was observed in association with the injection of albutrepenonacog alfa.

5.7 Other toxicity studies

5.7.1 *In vivo* thrombogenicity test in rabbits (CTD 4.2.3.7.7.1, Study S22456)

Albutrepenonacog alfa 0 (physiological saline), 75, 150, or 500 IU/kg/day was administered intravenously to rabbits (n=3/sex/group). The thrombogenic potential was assessed with a modified Wessler model of venous stasis (*Thromb Res.* 1980;17:353-366), and no thrombogenicity was noted at any doses.

5.R Outline of the review by PMDA

PMDA's view:

No particular problems were identified in the submitted toxicity data. The omission of carcinogenicity studies is acceptable and justified by the ICH S6 (R1). The omission of reproductive toxicity studies is acceptable because persistent hypercoagulability state is known to be a risk factor for recurrent miscarriage (*Obstet Gynecol.* 2007;109:1146-1155) and because hypercoagulation due to excessive dosing of a coagulation factor in normal animals is very likely to affect the ontogenesis, differentiation, and development in the animals.

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

6.1 Biopharmaceutic studies and associated analytical methods

A one-stage clotting assay was used to determine the FIX activity in plasma.

6.2 Clinical pharmacology studies

The following study results were submitted as clinical pharmacology assessment data: a foreign phase I study (CTD 5.3.3.2.1, Study 2001); a foreign phase I/II study (CTD 5.3.5.2.1, Study 2004); the global phase II/III study (CTD 5.3.5.2.2, Study 3001); a foreign phase III study (CTD 5.3.5.2.3, Study 3002); and results of a population pharmacokinetic (PPK) analysis on data obtained from these studies (CTD 5.3.3.5.1).

6.2.1 Studies in patients

6.2.1.1 Foreign phase I study (CTD 5.3.3.2.1, Study 2001 [[redacted] 20[redacted] to [redacted] 20[redacted]])

Pharmacokinetics of albutrepenonacog alfa was evaluated in 25 patients with severe hemophilia B (FIX activity level ≤2%), aged ≥12 to ≤65 years, previously treated with a FIX product (for >150 exposure days), and without inhibitors. A single intravenous dose of albutrepenonacog alfa 25 IU/kg (9 subjects), 50 IU/kg (14 subjects), or 75 IU/kg (9 subjects) was administered, and plasma FIX activity levels were determined at 11 time points including baseline and the time points from 30 min to 336 hours post dose. Of the 25 subjects, 7 subjects received 2 different doses with an interval of ≥14 days: 3 subjects, 25 and 50 IU/kg; 1 subject, 25 and 75 IU/kg; and 3 subjects, 50 and 75 IU/kg. Of the 25 subjects treated with albutrepenonacog alfa, 15 subjects received a single intravenous dose of 50 IU/kg of their previous FIX product which they had received before their participation in this study, and plasma FIX activity levels were determined at 6 time points including baseline and the time points from 30 min to 48 hours post dose. Evaluable data were obtained from 22 subjects, and Table 9 shows the pharmacokinetic parameter data in the 22 subjects or in total of 40 subjects including duplication (7 subjects received albutrepenonacog alfa 25 IU/kg; 13, albutrepenonacog alfa 50 IU/kg; 8, albutrepenonacog alfa 75 IU/kg; and 12, their previous FIX product). The applicant stated that the $t_{1/2}$ of albutrepenonacog alfa was approximately 5 times that of previous FIX products.

Table 9. Pharmacokinetic parameters for albutrepenonacog alfa and previous FIX product (mean ± standard deviation [SD])

	Albutrepenonacog alfa			Previous FIX product
	25 IU/kg (n = 7)	50 IU/kg (n = 13)	75 IU/kg (n = 8)	50 IU/kg (n = 12)
IR[a)] [(IU/dL)/(IU/kg)]	1.65 ± 0.19	1.38 ± 0.28	1.08 ± 0.19	1.00 ± 0.23
C_{max} [a)] (IU/dL)	41.1 ± 5.3	69.3 ± 13.0	82.0 ± 14.3	49.8 ± 11.4
$AUC_{0-\infty}$ (h·IU/dL)	4658 ± 1398	7670 ± 1601	9345 ± 1849	1388 ± 302
CL (mL/h/kg)	0.57 ± 0.19	0.68 ± 0.15	0.84 ± 0.16	3.77 ± 0.83
V_{ss} (dL/kg)	0.86 ± 0.26	0.92 ± 0.15	1.20 ± 0.27	1.16 ± 0.27
$t_{1/2}$ (h)	118.4 ± 48.7	100.2 ± 19.9	103.7 ± 18.3	21.5 ± 3.8
MRT (h)	152.9 ± 39.1	138.3 ± 21.5	144.5 ± 19.5	31.3 ± 5.8

[a)] The values shown are corrected by subtracting baseline FIX activity level from the post dose FIX activity level.

6.2.1.2 Foreign phase I/II study (CTD 5.3.5.2.1, Study 2004 [[redacted] 20[redacted] to [redacted] 20[redacted]])

Pharmacokinetics of albutrepenonacog alfa was evaluated in 15 patients with severe hemophilia B (FIX activity level ≤2%), aged ≥12 to ≤65 years, previously treated with a FIX product (for >150 exposure days), and without inhibitors. A single intravenous dose of albutrepenonacog alfa 25 IU/kg was administered, and plasma FIX activity levels were determined at 10 time points including baseline and the time points from 30 min to 336 hours post dose. Pharmacokinetic parameter data in 13 subjects with evaluable data are shown in Table 10. The $t_{1/2}$ (94.8 ± 40.7 h) observed in this study was similar to that in Study 2001 (118.4 ± 48.7 h after 25 IU/kg was administered).

Table 10. Pharmacokinetic parameters for albutrepenonacog alfa (mean ± SD)

	Albutrepenonacog alfa 25 IU/kg (n = 13)
IR [a] [(IU/dL)/(IU/kg)]	1.45 ± 0.12
C_{max} [a] (IU/dL)	36.1 ± 2.9
$AUC_{0-\infty}$ (h·IU/dL)	3414 ± 412
CL (mL/h/kg)	0.74 ± 0.10
V_{ss} (dL/kg)	0.92 ± 0.26
$t_{1/2}$ (h)	94.8 ± 40.7
MRT (h)	126.5 ± 41.6

[a] The values shown are corrected by subtracting baseline FIX activity level from the post dose FIX activity level.

6.2.1.3 Global phase II/III study (CTD 5.3.5.2.2, Study 3001 [[redacted] 20[redacted] to [redacted] 20[redacted]])

Pharmacokinetics were studied, after albutrepenonacog alfa 50 IU/kg was administered, in 46 patients (including 10 Japanese) with severe hemophilia B (FIX activity level ≤2%), aged ≥12 to ≤65 years, previously treated with a FIX product (for >150 exposure days), and without inhibitors. A single intravenous dose of albutrepenonacog alfa 50 IU/kg was administered, and plasma FIX activity levels were determined at 10 time points including baseline and the time points from 30 min to 336 hours post dose. Of the 46 subjects treated with albutrepenonacog alfa 50 IU/kg, 12 subjects received a single intravenous dose of their previous FIX product 50 IU/kg, and plasma FIX activity levels were determined at 7 time points including baseline and the time points from 30 min to 48 hours post dose. Evaluable data were obtained from 45 subjects, except for 1 in whom data were unavailable due to a bleeding episode at pharmacokinetics evaluation, and Table 11 shows the pharmacokinetic parameter data in these subjects totaling a pharmacokinetic population of 57 subjects (45 including 10 Japanese received albutrepenonacog alfa 50 IU/kg; and 12, their previous FIX products). According to the applicant's explanation, the pharmacokinetic parameters in the Japanese subjects were similar to those in the overall study population, and $t_{1/2}$ of albutrepenonacog alfa was longer than that of previous FIX products.

Table 11. Pharmacokinetic parameters for albutrepenonacog alfa and previous FIX product (mean ± SD)

	Albutrepenonacog alfa 50 IU/kg		Previous FIX product 50 IU/kg (n = 12)
	Japanese subjects (n = 10)	Overall study population (n = 45)	
IR [a] [(IU/dL)/(IU/kg)]	1.26 ± 0.46	1.27 ± 0.30	0.98 ± 0.30
C_{max} [a] (IU/dL)	64.0 ± 22.6	63.9 ± 14.9	49.1 ± 15.0
$AUC_{0-\infty}$ (h·IU/dL)	6685 ± 1892	7176 ± 2118	1400 ± 427
CL (mL/h/kg)	0.80 ± 0.22	0.77 ± 0.26	3.93 ± 1.32
V_{ss} (dL/kg)	1.03 ± 0.15	1.02 ± 0.19	1.18 ± 0.34
$t_{1/2}$ (h)	94.6 ± 18.8	101.7 ± 22.1	21.6 ± 5.5
MRT (h)	133.0 ± 22.4	140.4 ± 27.4	31.3 ± 8.2

[a] The values shown are corrected by subtracting baseline FIX activity level from the post dose FIX activity level.

Pharmacokinetics were studied after albutrepenonacog alfa 50 IU/kg (the same dose as the initial one) was administered in 15 subjects who had received routine prophylaxis with albutrepenonacog alfa (administration of albutrepenonacog alfa on a regular basis to prevent bleeding episodes) for 6 months. The pharmacokinetic parameter data after the multiple doses were similar to those at the initial dosing, suggesting no effects of multiple doses on the pharmacokinetic parameters.

6.2.1.4 Foreign phase III study (CTD 5.3.5.2.3, Study 3002 [[redacted] 20[redacted] to [redacted] 20[redacted]])

Pharmacokinetics of albutrepenonacog alfa was evaluated in 27 patients with severe hemophilia B (FIX activity level ≤2%), aged <12 years, previously treated with a FIX product (for ≥50 exposure days [patients aged <6 years] or for ≥150 days [patients aged ≥6 to <12 years]), and without inhibitors. A single intravenous dose of albutrepenonacog alfa 50 IU/kg was administered, and plasma FIX activity levels were determined at 10 time points including baseline and the time points from 30 min to 336 hours post dose. Of the 27 subjects treated with albutrepenonacog alfa 50 IU/kg, 17 subjects received a single intravenous dose of 50 IU/kg of their previous FIX product, and plasma FIX activity levels were determined at 5 time points including baseline and the time points from 30 min to 48 hours post dose. Pharmacokinetic parameter data are shown in Table 12. The applicant stated that the pharmacokinetic parameter data were comparable between the subjects aged <6 years and subjects aged ≥6 to <12 years.

Table 12. Pharmacokinetic parameters for albutrepenonacog alfa and previous FIX products in children (mean ± SD)

	Albutrepenonacog alfa 50 IU/kg		Previous FIX product 50 IU/kg	
	Aged <6 years (n = 12)	Aged ≥6 to <12 years (n = 15)	Aged <6 years (n = 8)	Aged ≥6 to <12 years (n = 9)
IR [a] [(IU/dL)/(IU/kg)]	0.95 ± 0.24	1.06 ± 0.24	0.68 ± 0.14	0.79 ± 0.23
C_{max} [a] (IU/dL)	48.3 ± 9.2	52.9 ± 12.3	34.0 ± 7.3	39.3 ± 11.9
$AUC_{0-\infty}$ (h·IU/dL)	4583 ± 1522	5123 ± 1607	886 ± 621	890 ± 189
CL (mL/h/kg)	1.18 ± 0.33	1.06 ± 0.30	7.16 ± 2.79	5.81 ± 1.38
V_{ss} (dL/kg)	1.42 ± 0.34	1.32 ± 0.26	1.77 ± 0.44	1.43 ± 0.29
$t_{1/2}$ (h)	89.6 ± 11.2	92.8 ± 19.0	19.9 ± 8.0	17.7 ± 4.5
MRT (h)	122.8 ± 17.4	129.2 ± 24.6	27.7 ± 11.3	25.2 ± 5.4

[a] The values shown are corrected by subtracting baseline FIX activity level from the post dose FIX activity level.

6.2.2 PPK analysis (CTD 5.3.3.5.1)

A 2-compartment model (NONMEM software [version 7.3.0]) based PPK analysis was performed on the plasma FIX activity data (2555 pieces of data in total) obtained from the foreign phase I study (Study 2001), the foreign phase I/II study (Study 2004), the global phase II/III study (Study 3001), and the foreign phase III study (Study 3002). Body weight and weight-corrected dose were identified as significant covariates and a 2-compartment model with those significant covariates was selected as the final model of the pharmacokinetic profile of albutrepenonacog alfa. Plasma FIX activity after multiple doses of albutrepenonacog alfa was simulated with this model, yielding trough values as shown in Table 13. The simulation showed that the median trough level of plasma FIX activity exceeded 1% (1 IU/dL) for both regimens of "25 or 40 IU/kg once weekly" and "50 or 75 IU/kg once every 14 days" in all age groups. The lower limit of the 90% prediction interval exceeded 1% for all regimens in patients aged ≥12 years but was below 1% for all regimens in patients aged <12 years, except for "40 IU/kg once a week."

The applicant's discussion on the results of the simulation:

The WFH guidelines (*GUIDELINES FOR THE MANAGEMENT OF HEMOPHILIA*, WFH. 2012) recommend that the plasma coagulation activity level should be maintained at ≥1% during routine prophylaxis.

Since simulation results suggest that a trough level of ≥1% can be achieved in almost all patients aged ≥12 years, the proposed regimens of albutrepenonacog alfa "25 to 40 IU/kg once weekly" and "50 to 75 IU/kg once every 14 days" are considered appropriate for routine prophylaxis. The precautionary information will also be provided to advise that pediatric patients aged <12 years may require a higher dose of albutrepenonacog alfa than adults because of their lower trough levels than those aged ≥12 years.

Table 13. Median trough levels of plasma FIX activity based on simulation (%) [90% prediction interval]

	Aged <6 years	Aged ≥6 to <12 years	Aged ≥12 to <18 years	Aged ≥18 years
25 IU/kg/week	2.6 [0.8, 6.0]	4.3 [1.6, 9.4]	6.4 [2.7, 13.1]	7.7 [3.3, 15.2]
40 IU/kg/week	4.9 [1.7, 10.7]	7.9 [3.2, 16.5]	11.6 [5.1, 22.7]	13.9 [6.2, 26.3]
50 IU/kg/14 days	1.1 [0.2, 3.6]	2.1 [0.4, 6.2]	3.7 [1.0, 9.3]	4.6 [1.4, 11.2]
75 IU/kg/14 days	2.1 [0.4, 6.3]	3.9 [0.9, 10.6]	6.6 [1.9, 15.8]	8.2 [2.7, 18.8]

6.R Outline of the review by PMDA

PMDA's view:

The submitted data on clinical pharmacology have demonstrated that albutrepenonacog alfa has a longer half-life than those of currently available FIX products. The appropriateness of the proposed dosing regimen for routine prophylaxis is discussed in Section 7.R.5.2 because relevant factors including the dosing regimens specified in the clinical studies and the relationship between plasma FIX activity and the efficacy of albutrepenonacog alfa should be considered together.

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

The applicant submitted the results of the following studies as the efficacy and safety data: the foreign phase I study (CTD 5.3.3.2.1, Study 2001), the foreign phase I/II study (CTD 5.3.5.2.1, Study 2004), the global phase II/III study (CTD 5.3.5.2.2, Study 3001), the foreign phase III study (CTD 5.3.5.2.3, Study 3002) and the interim analysis of the global phase III study (CTD 5.3.5.2.4, Study 3003). The main clinical studies are listed in Table 14.

Table 14. List of main clinical studies

	Study No.	Phase	Countries (No. of study sites)	Subjects	No. of treated subjects	Outline of dosage and administration
Foreign study	2001	I	Austria ([redacted]), France ([redacted]), Germany ([redacted]), Israel ([redacted]), Italy ([redacted]), Spain ([redacted])	Patients with severe hemophilia B (aged ≥12 to ≤65 years)	25	A single dose of albutrepenonacog alfa 25, 50, or 75 IU/kg
Foreign study	2004	I/II	Bulgaria ([redacted]), Israel ([redacted])	Patients with severe hemophilia B (aged ≥12 to ≤65 years)	17 (4 in the on-demand treatment group; 13 in the routine prophylaxis group)	Routine prophylaxis group: Albutrepenonacog alfa 15-35 IU/kg, adjustable up to 75 IU/kg according to the subject's condition, once every 7 days. On-demand group: Albutrepenonacog alfa ≥25 IU/kg in the event of a bleeding episode.
Global study	3001	II/III	Austria ([redacted]), Bulgaria ([redacted]), France ([redacted]), Germany ([redacted]), Israel ([redacted]), Italy ([redacted]), Japan ([redacted]), Russia ([redacted]), Spain ([redacted]), US ([redacted])	Patients with severe hemophilia B (aged ≥12 to ≤65 years)	63 (40 in Arm 1; 23 in Arm 2)	Arm 1: Albutrepenonacog alfa once every 7 days at the same dose given at the end of Study 2004 or 35-50 IU/kg, adjustable up to 75 IU/kg according to the subject's condition; subsequently, switchable to 75 IU/kg once every 10 or 14 days if the specified criteria are met; and 35-50 IU/kg in the event of a bleeding episode. Arm 2: Albutrepenonacog alfa 35-50 IU/kg or more only in the event of a bleeding episode for a specified period; then 35-50 IU/kg, adjustable up to 75 IU/kg according to the subject's condition, once every 7 days; and 35-50 IU/kg in the event of a bleeding episode. In perioperative period: in accordance with the recommendations of the WFH guidelines.
Foreign study	3002	III	Australia ([redacted]), Austria ([redacted]), Canada ([redacted]), Czech ([redacted]), France ([redacted]), Germany ([redacted]), Israel ([redacted]), Italy ([redacted]), Russia ([redacted]), Spain ([redacted])	Patients with severe hemophilia B (aged <12 years)	27	Albutrepenonacog alfa 35-50 IU/kg, adjustable up to 75 IU/kg according to the subject's condition, once every 7 days; 35-50 IU/kg in the event of a bleeding episode; and in perioperative period, in accordance with the recommendations of the WFH guidelines.

Main clinical studies are summarized below. Results of pharmacokinetic evaluation in each study are provided in Section 6.2 "Clinical pharmacology studies."

7.1 Phase I study

7.1.1 Foreign phase I study (CTD 5.3.3.2.1, Study 2001 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A dose-escalation study was conducted to evaluate the safety and pharmacokinetics of albutrepenonacog alfa in patients with severe hemophilia B (FIX activity level ≤2%), aged ≥12 to ≤65 years, previously treated with a FIX product (for >150 exposure days), and without inhibitors (target sample size: 24 subjects [4 in 25 IU/kg group, 13 in 50 IU/kg group, and 4 in 75 IU/kg group]).

A single dose of albutrepenonacog alfa 25, 50, or 75 IU/kg was administered successively. The subsequent dose was given after the safety evaluation of 4 subjects in each dose level was completed. Subjects who received the 25, 50, 75 IU/kg dose were to receive an additional dose of 50, 75, and 50 IU/kg, respectively, at an interval of ≥10 days (amended to "≥14 days" during the study). (The protocol was amended during the study to allow any additional dose as long as the second dose was different from the initial dose.)

A total of 25 subjects (5 in 25 IU/kg group; 8 in 50 IU/kg group; 5 in 75 IU/kg group; 3 in 25 + 50 IU/kg group; 1 in 25 + 75 IU/kg group; 3 in 50 + 75 IU/kg group) were enrolled and were all included in the safety analysis set.

As for the safety, 22 adverse events occurred in 52% (13 of 25) of subjects by Day 14 after albutrepenonacog alfa administration. Adverse events occurring in ≥2 subjects in the overall study population are shown in Table 15.

Table 15. Adverse events occurring in ≥2 subjects in the overall study population (Safety analysis set, n = 25)

	Albutrepenonacog alfa					
	25 IU/kg (n = 9)		50 IU/kg (n = 14)		75 IU/kg (n = 9)	
	No. of subjects (%)	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	No. of events
Arthralgia	0 (0)	0	1 (7.1)	1	2 (22.2)	3
Joint injury	1 (11.1)	1	0 (0)	0	1 (11.1)	1
Limb injury	1 (11.1)	1	1 (7.1)	1	0 (0)	0
Headache	0 (0)	0	1 (7.1)	1	1 (11.1)	1
Nasopharyngitis	1 (11.1)	1	1 (7.1)	1	0 (0)	0

There were 4 adverse drug reactions observed in 3 subjects (1 event each of constipation, headache, feeling hot, and injection site erythema). All events resolved.

No deaths, serious adverse events, or adverse events leading to treatment discontinuation occurred during the study.

7.2 Phase I/II study

7.2.1 Foreign phase I/II study (CTD 5.3.5.2.1, Study 2004 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A non-randomized, open-label, comparative study was conducted to evaluate the safety and efficacy of albutrepenonacog alfa in patients with severe hemophilia B (FIX activity level ≤2%), aged ≥12 to ≤65 years, previously treated with a FIX product (for >150 exposure days), and without inhibitors (target sample size: 15 subjects [increased to 20 subjects during the study]).

The study population consisted of the following 2 groups. Subjects were assigned by the investigators to either group and were given albutrepenonacog alfa for ≥20 weeks.

• Routine prophylaxis group

Subjects received albutrepenonacog alfa once every 7 days at an initial dose determined individually to be 15 to 35 IU/kg based on pharmacokinetic data, etc. Subsequently, the dose was adjusted according to the subject's condition (maximum 75 IU/kg). If the dose reached 75 IU/kg, the dosing interval was allowed to be shortened as needed. In the event of a bleeding episode, the dose of albutrepenonacog alfa required for hemostasis was to be calculated from individual pharmacokinetic data in accordance with the recommendations of the WFH guidelines, and the subject was treated at a dose of ≥25 IU/kg.

• On-demand treatment (treatment for hemostasis) group

In the event of a bleeding episode, the subject was treated with albutrepenonacog alfa ≥25 IU/kg. The dose required for hemostasis was calculated from individual pharmacokinetic data in accordance with the recommendations of the WFH guidelines.

A total of 17 subjects (13 in routine prophylaxis group; 4 in on-demand treatment group) were enrolled in this study and were all included in the safety and efficacy analysis sets.

The number of days exposed to albutrepenonacog alfa per subject (mean ±SD) was 13.0 ± 0.8 days (range, 12-14 days) in the on-demand treatment group and 51.5 ± 4.4 days (range, 45-59 days) in the routine prophylaxis group.

As for efficacy of routine prophylaxis, the median AsBR (range) was 1.1 (0.0-4.5)/subject-year in the routine prophylaxis group and 22.2 (16.6-25.9)/subject-year in the on-demand treatment group, showing a lower value in the routine prophylaxis group than in the on-demand treatment group.

A total of 46 adverse events occurred in 82.4% (14 of 17) of subjects. Adverse events occurring in ≥2 subjects are shown in Table 16 as the safety profile.

Table 16. Adverse events occurring in ≥2 subjects (Safety analysis set, n = 17)

Adverse event	No. of subjects (%)	No. of event	Adverse event	No. of subjects (%)	No. of event
Arthralgia	5 (29.4)	11	Hand fracture	2 (11.8)	2
Headache	3 (17.6)	3	Laceration	2 (11.8)	2
Upper respiratory tract infection	2 (11.8)	4			

No adverse drug reactions, deaths, serious adverse events, or adverse events leading to treatment discontinuation occurred during the study.

7.3 Phase III studies

7.3.1 Global phase II/III study (CTD 5.3.5.2.2, Study 3001 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A non-randomized, open-label, comparative study was conducted to evaluate the efficacy and safety of albutrepenonacog alfa in patients with severe hemophilia B (FIX activity level ≤2%), aged ≥12 to ≤65 years,

previously treated with a FIX product (for >150 exposure days), and had no inhibitors (target sample size: 60 subjects [35 in Arm 1, 25 in Arm 2]).

The study population consisted of the following 2 arms.

• Arm 1: Subjects enrolled were those on routine prophylactic FIX-product treatment before this study.

Subjects who completed Study 2004 stayed on the same weekly albutrepenonacog alfa dose they received at the end of Study 2004. Subjects who did not complete Study 2004 received albutrepenonacog alfa at a dose of 35 to 50 IU/kg once every 7 days. The dose was allowed to be increased gradually by 5 to 15 IU/kg up to 75 IU/kg in subjects who experienced at least 1 spontaneous bleeding episode. After administration for ≥26 weeks in the subjects who completed Study 2004 and for ≥30 weeks in the subjects who did not, they were able to switch to a higher dose regimen or a longer interval dosing regimen upon their request, as described in Table 17, if the following criteria were met: 1) no dose adjustment in the previous 1 month; and 2) no experience of spontaneous bleeding in the previous 1 month. The treatment interval was allowed to be shortened in subjects who experienced 2 spontaneous bleeding episodes after extending the dosing interval. In the event of a bleeding episode, the dose of albutrepenonacog alfa required for hemostasis was calculated from individual pharmacokinetic data in accordance with the recommendations of the WFH guidelines, and the subject was treated at a dose of 35 to 50 IU/kg, which was adjustable (maximum 75 IU/kg).

Table 17. Rules for switching regimen

Dose administered at 7-day intervals	Newly prescribed dose and treatment interval	Treatment period
≤40 IU/kg	75 IU/kg/14 days	≥30 weeks and >50 exposure days
>40 to ≤50 IU/kg	75 IU/kg/10 days	
>50 IU/kg	Regimen switching not allowed	>50 exposure days

• Arm 2: Subjects enrolled were those receiving only on-demand FIX-product treatment before this study.

Subjects in Arm 2 were treated with albutrepenonacog alfa by on-demand treatment only for bleeding episodes without receiving routine prophylactic treatment until either completing 26 weeks of on-demand treatment or experiencing 12 spontaneous bleeding episodes, whichever came first. Subjects then received routine treatment with albutrepenonacog alfa at a dose of 35 to 50 IU/kg once every 7 days for ≥30 weeks (during the study, the routine prophylactic treatment period was changed to ≥26 weeks). (The protocol was amended during the study as follows: the prophylactic dose for a subject in Arm 2 may be adjusted to a maximum of 75 IU/kg during the first 4 weeks, and the dose prescribed after 4 weeks of prophylactic treatment was to be maintained for the rest of the study.) In the event of a bleeding episode, the dose of albutrepenonacog alfa required for hemostasis was to be calculated from individual pharmacokinetic data in accordance with the recommendations of the WFH guidelines, and the subject was to be treated at a dose of 35 to 50 IU/kg, which was adjustable (maximum 75 IU/kg).

If subjects underwent surgery during the study, the efficacy and safety data of the perioperative treatment with

albutrepenonacog alfa were collected. In the perioperative period, albutrepenonacog alfa was to be administered before, after, and as appropriate, during the surgery in accordance with the recommendations of the WFH guidelines.

A total of 63 subjects (40 [including 6 Japanese] in Arm 1; and 23 [including 4 Japanese] in Arm 2) were enrolled in this study and were all included in the safety and efficacy analysis sets. Of 23 subjects in Arm 2, 19 (including 3 Japanese) who received 1 or more doses as on-demand treatment and in prophylaxis period were included in the primary efficacy analysis set. Data were collected in the perioperative period from 4 subjects (including no Japanese).

The number of days exposed to albutrepenonacog alfa per subject (mean ± SD) was 72.4 ± 22.1 days (range, 4-103 days) in Arm 1 and 51.5 ± 30.6 days (range, 4-91 days) in Arm 2.

The primary endpoint was the AsBR. In order to evaluate the efficacy of routine prophylaxis, the AsBR during the period in which only on-demand treatment was provided for bleeding episodes was compared to the AsBR during the subsequent period in which routine prophylaxis with albutrepenonacog alfa was performed (Table 18).

Table 18. AsBR (Primary efficacy analysis set, 19 subjects in Arm 2)

		On-demand treatment period (n = 19)	Routine prophylaxis period (n = 19)
Duration of treatment (days) (mean ± SD)		184.2 ± 20.6	315.7 ± 176.7
No. of subjects with any spontaneous bleeding episode		19 (100%)	9 (47.4%)
No. of spontaneous bleeding episodes requiring treatment		135	11
AsBR (bleeding episodes/ subject-year)	Mean ± SD	14.57 ± 8.42	0.73 ± 1.17
	Median [range]	15.4 [2.0, 39.5]	0.0 [0.0, 4.2]
Intergroup ratio of AsBR [95% confidence interval]		0.04 [0.019, 0.089]	
P-value [a)]		< 0.0001	

[a)] By Wilcoxon signed-rank sum test (the null hypothesis: the ratio of AsBR [routine prophylaxis/on-demand treatment] ≥0.50)

The median AsBR (range) of 3 Japanese subjects in the primary efficacy analysis set was 16.7 (2.0-19.6) bleeding episodes/subject-year during the on-demand treatment-only period and 1.6 (0.0-2.3) bleeding episodes/subject-year during the routine prophylaxis period.

In addition, the efficacy of albutrepenonacog alfa in routine prophylaxis with an extended treatment interval, the efficacy in on-demand treatment, and the efficacy in perioperative treatment were evaluated in an exploratory manner.

In 40 subjects in Arm 1, the median AsBR (range) was 0.0 (0.0-4.5) bleeding episodes/subject-year during the

7-day interval regimen. Of the 40 subjects, 26 were switched to another interval regimen at least once, and 7 and 21 received the 10-day and 14-day interval regimens, respectively; of these, 2 received both 10-day and 14-day interval regimen as a result of switching more than once. The median AsBR (range) during the 10-day and 14-day interval regimens was 0.0 (0.0-0.9) and 0.0 (0.0-7.3) bleeding episodes/subject-year, respectively. In 6 Japanese subjects enrolled in Arm 1, the median AsBR (range) during the 7-day interval regimen was 1.9 (0.0-4.5) bleeding episodes/subject-year. Of the 6 Japanese subjects, 2 were switched to another dosing interval regimen: none received the 10-day interval regimen, and 2 received the 14-day interval regimen. The median AsBR (range) during the 14-day interval regimen was 0.4 (0.0-0.8) bleeding episodes/subject-year.

As for the efficacy for on-demand treatment, a total of 358 bleeding episodes were treated with albutrepenonacog alfa. Of those, 98.6% (353 of 358 episodes) were treated successfully with 1 or 2 injections of albutrepenonacog alfa. Hemostatic efficacy of albutrepenonacog alfa was assessed by the investigators based on a 4-point ordinal scale shown in Table 19. Treatment with albutrepenonacog alfa was assessed as "excellent" or "good" in 94.1% (337 of 358 episodes). In Japanese subjects, albutrepenonacog alfa was administered in a total of 50 bleeding episodes, and 96.0% (48 of 50 episodes) of them were treated successfully with 1 or 2 injections. Treatment with albutrepenonacog alfa was assessed as "excellent" or "good" in 96.0% (48 of 50 episodes) in the Japanese subjects.

Table 19. Criteria to assess hemostatic efficacy of on-demand treatment

Excellent	Definite pain relief and/or unequivocal improvement in objective signs of bleeding at approximately 24 hours after the first injection and no additional injection required in order to achieve hemostasis.
Good	Definite pain relief and/or improvement in signs of bleeding at approximately 24 hours after the first injection, but a second injection required to achieve hemostasis.
Moderate	Probable or slight beneficial effect on pain relief and/or improvement in signs of bleeding at 24 hours after the first injection, and more than 2 additional injections required to achieve hemostasis.
Poor/No Response	No improvement at all or condition worsened at 24 hours after the first injection, and additional hemostatic intervention such as other FIX products or plasma preparations required to achieve hemostasis.

Hemostatic efficacy of perioperative treatment with albutrepenonacog alfa was assessed by the surgeons based on a 4-point ordinal scale shown in Table 20. Four subjects underwent 6 surgical procedures (2 knee replacements, 1 mastectomy, 1 rectal prolapse repair/hemorrhoidectomy, 1 wisdom teeth extraction, 1 tooth extraction), and the hemostatic efficacy of albutrepenonacog alfa was assessed as "excellent" or "good" in all surgeries.

Table 20. Criteria to assess hemostatic efficacy of perioperative treatment

Excellent	Hemostasis clinically not markedly different from normal (the degree of hemostasis achieved comparable to that expected during similar surgery in a non-hemophilic patient) or actual blood loss in surgery ≤120% of the expected blood loss.
Good	Normal or mildly abnormal hemostasis in terms of quantity and/or quality (slight oozing, prolonged time to hemostasis with increased bleeding compared to a non-hemophilic patient) or actual blood loss in surgery >120% but ≤130% of the expected blood loss.
Moderate	Moderately abnormal hemostasis in terms of quantity and/or quality (moderate hemorrhage difficult to control) with expected blood loss in surgery greater than that defined as in Good.
Poor/No Response	Severely abnormal hemostasis in terms of quantity and/or quality (severe hemorrhage difficult to control) and/or additional hemostatic intervention required with other FIX products or plasma preparations for complete hemostasis.

A total of 347 adverse events occurred in 85.7% (54 of 63) of subjects during the study period excluding the perioperative period. Adverse events occurring in ≥5% of subjects in the overall study population are shown in Table 21.

Table 21. Adverse events occurring in ≥5% of subjects (Safety analysis set, n = 63)

	No. of subjects (%)	No. of events		No. of subjects (%)	No. of events
Nasopharyngitis	16 (25.4)	38	Bronchitis	5 (7.9)	5
Headache	15 (23.8)	34	Pharyngitis	5 (7.9)	5
Arthralgia	9 (14.3)	19	Diarrhoea	5 (7.9)	6
Influenza	7 (11.1)	10	Toothache	5 (7.9)	5
Back pain	6 (9.5)	8	Synovitis	4 (6.3)	7
Limb injury	6 (9.5)	8	Contusion	4 (6.3)	8
Upper respiratory tract infection	5 (7.9)	7	Dizziness	4 (6.3)	5

During the study period excluding the surgical period, 11 adverse drug reactions (rash [5 events], headache [2 events], and 1 event each of dizziness, injection site haematoma, hypersensitivity, eczema) occurred in 5 subjects. All events resolved, but study treatment was discontinued in 2 subjects (one with hypersensitivity, the other with headache). No deaths occurred, but serious adverse events occurred in 2 subjects (one with synovitis, the other with acquired epileptic aphasia). Both events were assessed as unrelated to albutrepenonacog alfa and reported as resolved.

In perioperative period, 4 subjects experienced 5 adverse events (1 event each of anaemia, urinary tract infection, gastrointestinal injury, dental caries, and procedural pain). All events were assessed as unrelated to albutrepenonacog alfa and reported as resolved.

In 10 Japanese subjects, 55 adverse events occurred in 100% (10 of 10 subjects) during the study. Adverse events occurring in ≥2 Japanese subjects were nasopharyngitis (10 events in 4 subjects), back pain (4 events in 3 subjects), contusion (4 events in 2 subjects), injury (3 events in 2 subjects), diarrhoea (2 events in 2 subjects), gingivitis (2 events in 2 subjects), and eczema (2 events in 2 subjects). One subject experienced 3 adverse drug reactions (headache [2 events] and eczema [1 event]), and all events were reported resolved. This subject was withdrawn from the study due to headache. No serious adverse events occurred.

7.3.2 Foreign phase III study (5.3.5.2.3, Study 3002 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An uncontrolled study was conducted to evaluate the pharmacokinetics, safety, and efficacy of albutrepenonacog alfa in patients with severe hemophilia B (FIX activity level ≤2%), aged <12 years, previously treated with a FIX product (for ≥50 exposure days [patients aged <6 years] or for ≥150 days [patients aged ≥6 to <12 years]), and without inhibitors (target sample size, 22-24).

Subjects received routine prophylaxis with albutrepenonacog alfa 35 to 50 IU/kg once every 7 days for 48 weeks. The dose was allowed to be gradually increased by 5 to 15 IU/kg up to 75 IU/kg in subjects who

experienced at least 1 spontaneous bleeding episode. In the event of a bleeding episode, the dose of albutrepenonacog alfa required for hemostasis was calculated from individual pharmacokinetic data in accordance with the recommendations of the WFH guidelines, and the subject was treated at 35 to 50 IU/kg, which was adjustable (maximum 75 IU/kg). For subjects undergoing surgery, albutrepenonacog alfa was administered before and, as appropriate, during and after the surgery in accordance with the recommendations of the WFH guidelines.

A total of 27 subjects (12, aged <6 years; 15, aged ≥6 and <12 years) were enrolled in this study, and were all included in the safety and efficacy analysis sets.

The number of days exposed to albutrepenonacog alfa per subject (mean ± SD) was 61.9 ± 12.6 days (range, 42- 94 days).

Of a total of 106 bleeding episodes treated with albutrepenonacog alfa in on-demand basis during the study, 97.2% (103 of 106 episodes) were treated successfully with 1 or 2 injections of albutrepenonacog alfa. Hemostatic efficacy of albutrepenonacog alfa was assessed by the investigators based on 4-point ordinal scales shown in Tables 22 and 23. Treatment with albutrepenonacog alfa was assessed as “excellent” or “good” in 96.2% (100 of 104) of mild/moderate bleeding episodes (104 episodes) and as “good” for all severe bleeding episodes (2 episodes).

Hemostatic efficacy of perioperative treatment with albutrepenonacog alfa was assessed by the surgeons based on a 4-point ordinal scale shown in Table 24. Two subjects underwent 2 surgical procedures (2 tooth extraction operations), and the hemostatic efficacy of albutrepenonacog alfa was assessed as “excellent” or “good” for both surgeries.

Table 22. Criteria to assess hemostatic efficacy of on-demand treatment (mild to moderate bleeding episodes)

Excellent	No additional injections required to achieve hemostasis. Unequivocal improvement in objective signs of bleeding (swelling, tenderness, and/or decreased range of motion in the case of musculoskeletal hemorrhage) at 24 hours after the first injection.
Good	A second injection required to achieve hemostasis. Improvement in signs of bleeding at 24 hours after the first injection.
Moderate	More than 2 injections required to achieve hemostasis. Slight improvement in signs of bleeding at 24 hours after the first injection.
Poor/No Response	Additional hemostatic intervention with other FIX products or plasma preparations required to achieve hemostasis. No improvement at all or condition worsened (signs of bleeding) at 24 hours after the first injection.

Table 23. Criteria to assess hemostatic efficacy of on-demand treatment (severe or life-threatening bleeding episodes)

Excellent	Hemostasis clinically not markedly different from normal (the degree of hemostasis achieved comparable to that expected for a similar level of bleeding in a non-hemophilic patient) even in the absence of other hemostasis intervention.
Good	Normal or mildly abnormal hemostasis in terms of quantity and/or quality (slight oozing, prolonged time to hemostasis with increased bleeding compared to a non-hemophilic patient) even in the absence of other hemostasis intervention.
Moderate	Moderately abnormal hemostasis in terms of quantity and/or quality (moderate hemorrhages difficult to control).
Poor/No Response	Severely abnormal hemostasis in terms of quantity and/or quality (severe hemorrhage difficult to control) and/or additional hemostatic intervention required with other FIX products, cryoprecipitate, or plasma preparations more than expected.

Table 24. Criteria to assess hemostatic efficacy of perioperative treatment

Excellent	Hemostasis clinically not markedly different from normal (achieved hemostasis comparable to that expected during similar surgery in a non-hemophilic patient) even in the absence of other hemostasis intervention.
Good	Normal or mildly abnormal hemostasis in terms of quantity and/or quality (slight oozing, prolonged time to hemostasis with increased bleeding compared to a non-hemophilic patient) even in the absence of other hemostasis intervention.
Moderate	Moderately abnormal hemostasis in terms of quantity and/or quality (moderate hemorrhage difficult to control).
Poor/No Response	Severely abnormal hemostasis in terms of quantity and/or quality (severe hemorrhage difficult to control) and/or additional hemostatic intervention required with other FIX products or plasma preparations more than expected.

As for efficacy during routine prophylaxis, the median AsBR (range) was 0.0 (0.0-3.5) bleeding episodes/subject-year.

As for safety, a total of 152 adverse events occurred in 96.3% (26 of 27) of subjects. Adverse events occurring in ≥5% of subjects are shown in Table 25.

Table 25. Adverse events occurring in ≥5% of subjects (Safety analysis set, n = 27)

	No. of subjects (%)	No. of events		No. of subjects (%)	No. of events
Pyrexia	9 (33.3)	14	Pharyngitis	2 (7.4)	3
Contusion	5 (18.5)	9	Viral infection	2 (7.4)	3
Nasopharyngitis	4 (14.8)	6	Molluscum contagiosum	2 (7.4)	2
Arthralgia	4 (14.8)	5	Upper respiratory tract infection	2 (7.4)	2
Cough	4 (14.8)	4	Dental discomfort	2 (7.4)	2
Bronchitis	3 (11.1)	4	Diarrhoea	2 (7.4)	2
Ear infection	3 (11.1)	4	Toothache	2 (7.4)	2
Gastroenteritis	3 (11.1)	3	Vomiting	2 (7.4)	2
Head injury	3 (11.1)	3	Pain in extremity	2 (7.4)	2
Injury	2 (7.4)	4	Oropharyngeal pain	2 (7.4)	2
Headache	2 (7.4)	4	Anaemia	2 (7.4)	2

No adverse drug reactions occurred during the study. Four subjects experienced 6 serious adverse events (arthralgia [2 events] and 1 event each of forearm fracture, groin pain, head injury, tongue injury) and recovered from these events. No deaths or adverse events leading to treatment discontinuation occurred.

7.R Outline of the review by PMDA

7.R.1 Review policy

7.R.1.1 Efficacy and safety evaluation

Epidemiological characteristics, pathological conditions of bleeding tendency, and the treatment concept of FIX replacement therapy to control and prevent bleeding episodes in FIX deficient patients including those with hemophilia B are similar in and out of Japan. This suggests that intrinsic and extrinsic ethnic factors are unlikely to affect the efficacy and safety of albutrepenonacog alfa significantly. Therefore, in regard to the efficacy of albutrepenonacog alfa, PMDA considered the data from Study 3001, a global study, as the pivotal study as well as data from Study 3002, a study in children aged <12 years, to evaluate the preventive effect of routine prophylaxis with albutrepenonacog alfa on bleeding tendency and the hemostatic effect of on-demand treatment with albutrepenonacog alfa. In regard to the safety of albutrepenonacog alfa, PMDA reviewed all data from the submitted clinical studies on the occurrence of adverse events, development of inhibitors, and other relevant parameters.

7.R.2 Efficacy

7.R.2.1 Efficacy for on-demand treatment of bleeding episodes

The percentage of bleeding episodes successfully treated with 1 or 2 injections of albutrepenonacog alfa was 98.6% (353 of 358 episodes) in Study 3001 (subjects aged ≥12 to ≤65 years) and 97.2% (103 of 106 episodes) in Study 3002 (subjects aged <12 years). The percentage of bleeding episodes assessed as "excellent" or "good" according to the predefined 4-point ordinal scales was 94.1% (337 of 358 episodes) in Study 3001, 96.1% (100 of 104 episodes) for mild/moderate bleeding in Study 3002, and 100% (2 of 2 episodes) for severe bleeding in Study 3002.

In light of the fact that highly effective hemostasis was achieved with the use of albutrepenonacog alfa in both clinical studies, PMDA concluded that albutrepenonacog alfa is expected to be effective in on-demand treatment of bleeding episodes in patients including children.

7.R.2.2 Efficacy of perioperative treatment

Hemostatic efficacy of albutrepenonacog alfa for perioperative treatment was assessed according to the predefined 4-point ordinal scales in Studies 3001 and 3002. As a result, the hemostatic efficacy was assessed as "excellent" or "good" for all 8 surgeries (6 in Study 3001, 2 in Study 3002).

In light of the facts that FIX replacement therapy is essential for surgery in FIX deficient patients and that the hemostatic effectiveness of albutrepenonacog alfa has been demonstrated, PMDA concluded that albutrepenonacog alfa is expected to be effective in controlling perioperative bleeding in patients including children.

7.R.2.3 Efficacy of routine prophylaxis

In Study 3001, the AsBR was compared between on-demand treatment and routine prophylaxis at 7-day

intervals, the primary efficacy endpoints in Arm 2, and the results showed a statistically significant difference between them (Table 18). Furthermore, the median AsBR was 0.0 in subjects in Arm 1 of Study 3001, regardless of the dosing interval of albutrepenonacog alfa, and was 0.0 also in subjects of Study 3002 (Table 26).

Table 26. Summary of AsBR (bleeding episodes/subject-year) in Studies 3001 and 3002

	Study 3001: Arm 2 (Primary efficacy analysis set)		Study 3001: Arm 1 (Efficacy analysis set)			Study 3002 (Efficacy analysis set)
	On-demand (n = 19)	7-day interval (n = 19)	7-day interval (n = 40)	10-day interval (n = 7)	14-day interval (n = 21)	7-day interval (n = 27)
Median [range]	15.4 [2.0, 39.5]	0.0 [0.0, 4.2]	0.0 [0.0, 4.5]	0.0 [0.0, 0.9]	0.0 [0.0, 7.3]	0.0 [0.0, 3.5]

On the basis of the submitted clinical study data, PMDA concluded that albutrepenonacog alfa is expected to be effective in routine prophylaxis in patients including children.

7.R.2.4 Consistency between the overall study population and the Japanese population

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

Table 27 shows the results of efficacy evaluation (of on-demand treatment and routine prophylaxis) in the overall study population and the Japanese-only population in Study 3001. Since similar results were obtained for all efficacy endpoints in the overall study population and the Japanese population, PMDA concluded that the efficacy of albutrepenonacog alfa can also be expected in Japanese patients.

Table 27. Results of efficacy evaluation in Study 3001 (Efficacy analysis set)

	Efficacy endpoints		Japanese population		Overall study population	
			No. of subjects		No. of subjects	
On-demand treatment	Percentage of bleeding episodes successfully treated with 1 or 2 injections of albutrepenonacog alfa		10	96.0% (48 of 50 episodes)	63	98.6% (353 of 358 episodes)
	Percentage of bleeding episodes for which hemostatic efficacy was assessed as "excellent" or "good"		10	96.0% (48 of 50 episodes)	63	94.1% (337 of 358 episodes)
Routine prophylaxis	Median AsBR (bleeding episodes/ subject-year) [range]	Arm 2 (on-demand treatment)	4	11.2 [2.0, 19.6]	23	11.6 [0.0, 39.5]
		Arm 2 (7-day interval routine prophylaxis)	3	1.6 [0.0, 2.3]	19	0.0 [0.0, 4.2]

7.R.3 Safety

7.R.3.1 Safety of albutrepenonacog alfa

In the clinical studies excluding Study 3003, 75 of 107 subjects treated with albutrepenonacog alfa received the drug for ≥50 exposure days. The following serious adverse events were reported: 2 events (synovitis and acquired epileptic aphasia) in 2 subjects in Study 3001; 6 events (arthralgia [2 events] and 1 event each of

forearm fracture, groin pain, head injury, tongue injury) in 4 subjects in Study 3002; and 6 events (head injury [2 events] and 1 event each of oesophagitis, colonic polyp, post-traumatic extradural haematoma, iron deficiency anaemia) in 5 subjects, as of [redacted], 20[redacted], in Study 3003, which is currently conducted as an extension study of Studies 3001 and 3002. All events were assessed as unrelated to the study drug. The applicant claimed that the safety and tolerability of albutrepenonacog alfa were good.

The applicant's explanation on the safety in children:
In Study 3002, the incidence of adverse events in subjects aged <12 years was 96.3% (26 of 27 subjects), which was higher than that in subjects aged ≥12 to ≤65 years in Studies 2001, 2004, and 3001 (85.0% [68 of 80 subjects]). Adverse events that occurred in subjects aged <12 years at a markedly higher incidence than that in those aged ≥12 years were events associated with pyrexia, infections, and injuries. All adverse events reported in subjects aged <12 years, including 6 serious adverse events in 4 subjects, were assessed as unrelated to albutrepenonacog alfa. No development of inhibitors to FIX was reported in the clinical studies conducted so far. There is no significant difference in the safety profile of albutrepenonacog alfa between subjects aged ≥12 and <12 years, and thus albutrepenonacog alfa is also considered well tolerated in subjects aged <12 years.

PMDA's view:
No difference in the safety profile of albutrepenonacog alfa between children (<12 years of age) and adolescents (≥12 years of age) was found in the submitted clinical study data. Accordingly, the safety of albutrepenonacog alfa is considered acceptable in patients including children.

7.R.3.2 Adverse events reported in patients treated with currently available FIX products
Development of FIX inhibitors, shock/anaphylaxis, and serious thromboembolic events have been reported in association with currently available FIX products. Such events were not noted in any of the clinical studies of albutrepenonacog alfa, and no other clinically significant adverse events in these studies were found.

PMDA's view:
Precautionary statements concerning inhibitor development, shock/anaphylaxis, and thromboembolic events should be provided in the package insert and other materials for albutrepenonacog alfa. Information on development of inhibitors is considered very important because occurrence of anaphylaxis and allergic reactions during treatment with a currently available FIX product was reported in some patients with hemophilia B and inhibitors (*J Pediatr Hematol Oncol.* 1997;19:23-27, *Textbook of Hemophilia.* 3rd ed. Wiley Blackwell. 2014;103-106) and because the inhibitors may neutralize the efficacy of albutrepenonacog alfa. The applicant should provide, in an immediate and proper manner, the information obtained from their ongoing clinical studies and in the post-marketing setting to healthcare professionals in clinical settings.

7.R.4 Indication

On the basis of the results of clinical studies to evaluate the on-demand treatment, perioperative treatment, and routine prophylaxis with albutrepenonacog alfa in patients with hemophilia B with a FIX activity ≤2%, PMDA concluded that the efficacy of albutrepenonacog alfa can be expected and that the clinical position of albutrepenonacog alfa should be comparable to currently available FIX products. Accordingly, PMDA concluded that albutrepenonacog alfa should be indicated for "control of bleeding tendency in patients with blood coagulation factor IX deficiency" as is the case for currently available FIX products.

7.R.5 Dosage and administration

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

The applicant's explanation on the dosage and administration selected for on-demand treatment:

In the event of a bleeding episode in Studies 3001 and 3002, the dose of albutrepenonacog alfa required for hemostasis was calculated in accordance with the recommendations of the WFH guidelines, and selected to be 35 to 50 IU/kg, which was adjusted up to 75 IU/kg. In light of the above, the following was proposed for the dosage and administration of albutrepenonacog alfa: "For treatment of acute bleeding, the product should be administered at the required dose calculated on the basis of the patient's body weight and the target increment of blood coagulation factor IX." The median initial dose (range) for the on-demand treatment was 46.7 (13.3-99.9) IU/kg in Study 3001 and 45.0 (25.8-76.4) IU/kg in Study 3002.

PMDA's view:

Taking into account the approximate median dose (50 IU/kg) in clinical studies and the dosing regimens of currently available recombinant FIX products, PMDA considers that the dosage and administration section should include a statement that the usual dose is 50 IU/kg, and the dose should be increased or decreased as appropriate according to the patient's condition. Since data on the efficacy of the use of albutrepenonacog alfa in surgeries were available from the clinical studies, albutrepenonacog alfa may be administered not only for "treatment of acute bleeding" but also for perioperative treatment.

7.R.5.2 Dosage and administration for routine prophylaxis

The applicant proposed the following dosages for routine prophylaxis:

The recommended starting dosages are (1) 25 to 40 IU/kg once every 7 days, and (2) 50 to 75 IU/kg once every 14 days. Subsequent doses and dosing intervals should be adjusted as appropriate according to the patient's condition and clinical response.

PMDA's view:

The applicant explained that the PPK analysis-based simulation showed that the trough level of FIX activity exceeded 1% after albutrepenonacog alfa 25 to 40 IU/kg was administered once every 7 days [see Section 6.2.2]. However, no clear consensus has been reached on the relationship between the trough level of >1% and the efficacy of albutrepenonacog alfa in routine prophylaxis. Thus, 25 to 40 IU/kg cannot be concluded to be appropriate dose range although the trough level is simulated to exceed 1%. Meanwhile, the efficacy and

safety of weekly routine prophylaxis with albutrepenonacog alfa have been demonstrated in Studies 3001 and 3002 conducted in patients aged ≥12 and <12 years, respectively, with the starting dose of albutrepenonacog alfa being 35 to 50 IU/kg. In light of the above, the appropriate usual dosage should be "35 to 50 IU/kg once every 7 days" regardless of age, based on the dosage selected for the studies. Also, it is acceptable to specify that the dose is adjustable as appropriate individually as in the clinical studies, unless it exceeds 75 IU/kg.

In regard to 14-day interval regimen, the following subjects were allowed to switch from once every 7-day to 75 IU/kg once every 14-day regimen in Study 3001: those who were on a stable dose of ≤40 IU/kg in once every 7-day routine prophylaxis and who had no spontaneous bleeding episode in the previous 1 month. Therefore, it is acceptable that the Dosage and Administration section specifies an adjustable dosage regimen, if the following dosage adjustment rule employed in the clinical studies is disclosed: the dosing interval was allowed to be switched from once every 7 days to once every 14 days in consideration of the patients' recent bleeding condition after starting once every 7-day routine prophylaxis. Since the dose of 75 IU/kg was evaluated also in subjects aged <12 years in a clinical study, switching to 75 IU/kg once every 14 days is considered acceptable in this patient population.

7.R.5.3 Injection rate

In Study 2004, albutrepenonacog alfa was specified to be administered at an injection rate of approximately 250 IU/min or over approximately 5 to 15 min. The actual injection rate and time was [redacted] IU/min and [redacted] min, respectively. The injection rate and time specified in Studies 3001 and 3002 were the same as those in Study 2004.

PMDA's view:

In the Dosage and Administration section, only "slowly injected intravenously" should be referred to instead of specific description of injection rate or time, since they were not clearly specified in the clinical studies. In light of the WFH guidelines' recommendation that "FIX concentrates should be infused by slow IV injection at a rate not to exceed a volume of 3 mL per minute in adults and 100 units per minute in young children," physicians should be informed of the risk of potential adverse events (e.g., injection site pain) due to an excessive injection rate.

As a result of the review in Sections 7.R.5.1 to 7.R.5.3, PMDA has reached a conclusion that the dosage and administration of albutrepenonacog alfa should be as follows:

Dosage and Administration

The product should be reconstituted with the entire volume of the supplied diluent, and then slowly injected intravenously.

The usual dose is 50 IU/kg body weight. The dose may be adjusted according to the patient's condition.

For routine prophylaxis, the usual dosage is 35 to 50 IU/kg body weight once every 7 days. Patients may be switched to 75 IU/kg body weight once every 14 days according to the patient's condition. Regardless of the dosing interval, the dose should be adjusted as appropriate and must not exceed 75 IU/kg body weight.

7.R.6 Post-marketing investigations

The applicant's explanation on the post-marketing surveillance of albutrepenonacog alfa:

A drug use-results survey is planned to be conducted to characterize the safety and efficacy of albutrepenonacog alfa in FIX deficient patients (target sample size, 70 subjects; and observation period, 2 years) in routine clinical practice. The target sample size was determined as a feasible number of patients enrolled during the 4-year registration period of the surveillance based on the anticipated number of patients treated with albutrepenonacog alfa in the post-marketing setting in Japan. Occurrence of adverse events including the following will be investigated in this surveillance: shock, anaphylaxis, thromboembolism, and development of inhibitors.

PMDA's view:

Only a limited number of Japanese subjects were evaluated in the clinical studies of albutrepenonacog alfa, and treatment experience with albutrepenonacog alfa is also limited in clinical settings in Japan. These facts warrant the implementation of a post-marketing surveillance in routine clinical practice. It is important that the safety data to be collected from patients in the post-marketing surveillance should be evaluated, for instance, in comparison with the safety data in the submitted clinical studies to consider whether to collect further data.

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 5.3.5.2.2, CTD 5.3.5.2.4) 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 thus concluded that overall clinical studies were conducted in compliance with GCP and that there were no obstacles to conducting its review based on the submitted application documents. Although the impact on the evaluation of the entire study was small, the following was found with the sponsor, and a notification was issued to the applicant (sponsor) to improve it.

Matter to be improved:

Sponsor

- The sponsor did not properly prepare their standard operating procedures regarding compensation to the subject in the event of trial-related injuries at the time the clinical study started.

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

PMDA has concluded that the data submitted demonstrated the efficacy of albutrepenonacog alfa in controlling bleeding tendency in FIX deficient patients and acceptable safety in view of the benefits indicated by the data submitted. Also, albutrepenonacog alfa is considered to provide a clinically meaningful option for the treatment to control bleeding tendency in FIX deficient patients.

PMDA has concluded that albutrepenonacog alfa may be approved if the drug is not considered to have any particular problem based on a further review by Expert Discussion on issues including the efficacy, safety, and post-marketing surveillance.

Review Report (2)

August 22, 2016

Product Submitted for Approval

Brand Name	Idelvion I.V. Injection 250
	Idelvion I.V. Injection 500
	Idelvion I.V. Injection 1000
	Idelvion I.V. Injection 2000
Non-proprietary Name	Albutrepenonacog Alfa (Genetical Recombination)
Applicant	CSL Behring K.K.
Date of Application	December 17, 2015

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).

1.1 Efficacy

Based on the submitted clinical study data, PMDA has concluded that albutrepenonacog alfa is expected to be effective in on-demand treatment to stop bleeding, perioperative treatment, and routine prophylaxis to prevent bleeding in patients including children.

The PMDA's conclusion was supported by the expert advisors.

1.2 Safety

Based on information including the submitted clinical study data, PMDA has concluded that the safety of albutrepenonacog alfa is acceptable in patients including children. The PMDA's conclusion was supported by the expert advisors.

The applicant's explanation of the latest information on the development of inhibitors in ongoing Study CSL654_3003 (Study 3003):

Study 3003 was initially conducted as an extension study of Studies CSL654_3001 and CSL654_3002 (Study 3001 and Study 3002, respectively). During the study, however, the study protocol was amended to allow enrollment of patients with severe hemophilia B (blood coagulation factor IX [FIX] activity level ≤2%) who

were not previously treated with a FIX product. So far, 3 patients with no history of FIX product treatment have received albutrepenonacog alfa, and development of inhibitors was reported in 1 of the 3 patients. In this subject (aged 11 years), inhibitors were detected after the 13th dose of albutrepenonacog alfa, and routine prophylaxis with albutrepenonacog alfa was discontinued. The subject has not recovered from the event but is permitted to receive on-demand treatment with albutrepenonacog alfa for bleeding episodes. The current frequency of development of inhibitors in all subjects enrolled in Study 3003 is 1.1% (1 of 87 subjects).

PMDA's view on development of inhibitors to albutrepenonacog alfa:
In literature, the incidence of development of inhibitors to FIX products is reported to be 2% to 5% in patients with hemophilia B (*Haemophilia.* 2009;15:1027-1031, *Haemophilia.* 2014;20:25-31). With regard to albutrepenonacog alfa, development of inhibitors was reported in a subject in Study 3003, but at this point, definitive conclusions on the rate of development cannot be drawn from the limited number of subjects. Nevertheless, information on the subject should be provided to healthcare professionals in clinical settings to raise their attention. In addition, if new information is obtained from ongoing Study 3003 or in the post-marketing setting, the information should be provided immediately and appropriately.

The expert advisors commented that collecting post-marketing safety data including data on development of inhibitors is important and supported the PMDA's conclusion regarding inhibitors.

1.3 Indication

Based on the submitted clinical study data, PMDA considers that the clinical positioning of albutrepenonacog alfa is similar to the currently available FIX products and offers a treatment option. PMDA concluded that albutrepenonacog alfa should be indicated for "control of bleeding tendency in patients with blood coagulation factor IX deficiency" as is the case for currently available FIX products.

The PMDA's conclusion was supported by the expert advisors.

1.4 Dosage and administration

1.4.1 Dosage and administration for on-demand treatment to stop bleeding

In light of the approximate median dose (50 IU/kg) in Studies 3001 and 3002 and other relevant data, PMDA considered it appropriate to include the following statement: the usual dose is 50 IU/kg, and the dose should be adjusted according to the patient's condition. PMDA also considered it acceptable for albutrepenonacog alfa to be used in perioperative treatment because data showing efficacy in such use were obtained from the clinical studies.

The PMDA's conclusion was supported by the expert advisors.

1.4.2 Dosage and administration for routine prophylaxis

The following opinions were received from the expert advisors, who supported the PMDA's conclusion presented in Section 7.R.5.2 "Dosage and administration for routine prophylaxis" of the Review Report (1).

- The dose regimen in routine prophylaxis should be adjusted as appropriate according not only to tough levels but also to patient's condition, such as occurrence of bleeding. Consequently, the efficacy in routine prophylaxis is not explained by a trough level of >1% alone. The PMDA's conclusion is, therefore, appropriate in that the dose regimen of albutrepenonacog alfa should be based on the dose regimens of the clinical studies for which the efficacy and safety have been demonstrated.

1.4.3 Injection rate

Since the injection rate or time was not clearly specified in the clinical studies of albutrepenonacog alfa, PMDA considered that only "slowly injected intravenously" should be referred to in the Dosage and Administration section instead of specific description of injection rate or time.

The PMDA's conclusion was supported by the expert advisors.

Taking into account the expert discussion shown in Sections 1.4.1 to 1.4.3 above, PMDA instructed the applicant to modify the Dosage and Administration section as shown below.

Dosage and Administration
The product should be reconstituted with the entire volume of the supplied diluent, and then slowly injected intravenously.

The usual dose is 50 IU/kg body weight. The dose may be adjusted according to the patient's condition.

For routine prophylaxis, the usual dosage is 35 to 50 IU/kg body weight once every 7 days. Patients may be switched to 75 IU/kg body weight once every 14 days according to the patient's condition. Regardless of the dosing interval, the dose should be adjusted as appropriate and must not exceed 75 IU/kg body weight.

1.5 Risk management plan (draft)

In view of the discussions in "7.R.6 Post-marketing investigations" of the Review Report (1), PMDA considered that a post-marketing surveillance in actual clinical settings should be conducted. The safety data to be collected from the patients in the post-marketing surveillance should be evaluated, for instance, in comparison with the safety data in the submitted clinical studies to consider whether to collect further data.

The PMDA's conclusion was supported by the expert advisors.

The following opinions were received from the expert advisors:

- Because of limited safety data in children aged ≤12 years, such data should be collected continuously even after the marketing approval.
- Because of very limited data on development of inhibitors in patients who are not previously treated with a FIX product, such data should also be collected even after the marketing approval.
- Since albutrepenonacog alfa, unlike currently available FIX products, is a fusion protein linked with albumin, the possibility cannot be ruled out that adverse drug reactions other than those caused by currently available FIX products will occur. Attention should also be paid to the possibility of persistent adverse drug reactions associated with prolonged half-life of FIX. Therefore, it is important to collect post-marketing safety data.

In view of the above opinions from the expert advisors, PMDA concluded that the risk management plan (draft) for albutrepenonacog alfa should include the safety and efficacy specifications shown in Table 1, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities listed in Tables 2 and 3. The applicant agreed to take appropriate measures for the risk management plan (draft) accordingly.

Table 1. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
・Development of inhibitors	・Shock and anaphylaxis ・Thromboembolism	None
Efficacy specification		
Not applicable		

Table 2. Summary of additional pharmacovigilance activities and additional risk minimization activities included in the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
・Early post-marketing phase vigilance ・Use-results survey (see Table 3) ・Post-marketing clinical study (an extension study) [a)]	・Early post-marketing phase vigilance

[a)] After marketing authorization, the ongoing Study 3003 will be continued as a post-marketing clinical study until albutrepenonacog alfa will be commercially available in clinical settings.

Table 3. Outline of use-results survey (draft)

Objectives	To confirm the long-term safety and efficacy in routine clinical practice
Survey method	Central registration
Population	Patient with blood coagulation factor IX deficiency
Observation period	2 years
Planned sample size	70
Main survey items	Patient characteristics, status of treatment with albutrepenonacog alfa (including information on surgery in perioperative treatments), concomitant drugs/concomitant therapies, laboratory data, adverse events, and efficacy.

2. Overall evaluation

Based on the above review, PMDA has concluded that the product may be approved, with the following conditions, after modifying the indication and the dosage and administration as shown below. Since the product is a drug with a new active ingredient, the re-examination period is 8 years. Neither the drug

product nor its drug substance is classified as a poisonous drug or a powerful drug, and the product is classified as a biological product.

Indication

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

Dosage and Administration

The product should be reconstituted with the entire volume of the supplied diluent, and then slowly injected intravenously.

The usual dose is 50 IU/kg body weight. The dose may be adjusted according to the patient's condition.

For routine prophylaxis, the usual dosage is 35 to 50 IU/kg body weight once every 7 days. Patients may be switched to 75 IU/kg body weight once every 14 days according to their condition. Regardless of the dosing interval, the dose should be adjusted as appropriate and must not exceed 75 IU/kg body weight.

Conditions for Approval

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