

## Report on the Deliberation Results

March 10, 2015

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

[Brand name]                      NovoThirteen 2500 IU for Intravenous Injection  
[Non-proprietary name]        Catridecacog (Genetical Recombination) (JAN\*)  
[Applicant]                        Novo Nordisk Pharma Ltd.  
[Date of application]            August 29, 2014

### [Review results]

In the meeting held on March 5, 2015, the Second Committee on New Drugs concluded that the product may be approved and that its result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 10 years. Neither the drug substance nor the drug product is classified as a poisonous drug or a powerful drug and the product is not classified as a biological product or a specified biological product.

### [Conditions for approval]

The applicant is required to:

- Develop and appropriately implement a risk management plan.
- Conduct a use-results survey that should cover all Japanese patients receiving the product, to identify the characteristics of patients receiving the product, to collect efficacy and safety data, and to take appropriate measures to ensure the proper use of the product, wherever possible, since the number of subjects enrolled in the Japanese clinical studies of the product is extremely limited. The survey should be continued for a certain period of time.

\* *Japanese Accepted Name (modified INN)*

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

## Review Report

February 17, 2015

The 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]	NovoThirteen 2500 IU for Intravenous Injection
[Non-proprietary name]	Catridecacog (Genetical Recombination)
[Applicant]	Novo Nordisk Pharma Ltd.
[Date of application]	August 29, 2014
[Dosage form/Strength]	Lyophilized powder for solution for injection: One vial contains 2500 IU of Catridecacog (Genetical Recombination) to be reconstituted prior to administration.
[Application classification]	Prescription drug (1) Drug containing a new active ingredient
[Definition]	Catridecacog is a recombinant human blood coagulation factor XIII analog. Catridecacog is a protein composed of 2 A-subunits of human blood coagulation factor XIII consisting of 731 amino acid residues each.
[Structure]	See Attachment
[Items warranting special mention]	Orphan drug (Designation [26 yaku] No. 333, Notification No. 0513-1 from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated May 13, 2014) Prior assessment consultation was carried out for this drug.
[Reviewing office]	Office of Vaccines and Blood Products

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

Attachment

[Amino acid sequence]

```
SETSRTAFFG RRAVPPNNSN AAEDDLPTVE LQGVVPRGVN LQEFNLNVTSV  
HLFKERWDTN KVDHHTDKYE NNKLIVRRGQ SFYVQIDFSR PYDPRRDLFR  
VEYVIGRYPQ ENKGTIIPVP IVSELQSGKW GAKIVMREDR SVRLSIQSSP  
KCIVGKFRMY VAVWTPYGVL RTSRNPETDT YILFNPWCED DAVYLDNEKE  
REEYVLNDIG VIFYGEVNDI KTRSWSYGQF EDGILDTCLY VMDRAQMDLS  
GRGNPIKVSF VGSAMVNAKD DEGVLVGSWD NIYAYGVPPS AWTGSVDILL  
EYRSSENPRV YGQCWVFAGV FNTFLRCLGI PARIVTNYFS AHDNDANLQM  
DIFLEEDGNV NSKLTKDSVW NYHCWNEAWM TRPDLPVGFQ GWQAVDSTPQ  
ENSDGMYRCG PASVQAIKHG HVCFQFDAPF VFAEVNSDLI YITAKKDGTH  
VVENVDATHI GKLIIVTKQIG GDGMMDITDT YKFQEGQEEE RLALLETALMY  
GAKKPLNTEG VMKSRSNVDM DFEVENAVLG KDFKLSITFR NNSHNRYTIT  
AYLSANITFY TGVPKAEFFK ETFDVTLEPL SFKKEAVLIQ AGEYMGQLE  
QASLHFFVTA RINETRDVLA KQKSTVLTIP EIIIKVVRTQ VVGSDMTVTV  
EFTNPLKETL RNVVHLDGP GVTRPMKKMF REIRPNSTVQ WEEVCRPWVS  
GHRKLIASMS SDSLRHVYGE LDVQIQRRPS M
```

2

S1: Acetylation

Molecular formula and molecular weight:

$C_{7416}H_{11470}N_{2026}O_{2222}S_{56}$ : 166,356.30 (dimer)

$C_{3708}H_{5735}N_{1013}O_{1111}S_{28}$ : 83,178.15 (monomer)

## Review Results

February 17, 2015

[Brand name] NovoThirteen 2500 IU for Intravenous Injection

[Non-proprietary name] Catridecacog (Genetical Recombination)

[Applicant] Novo Nordisk Pharma Ltd.

[Date of application] August 29, 2014

[Review results]

Based on the data submitted by the applicant, PMDA has concluded that the efficacy of catridecacog in controlling bleeding tendency in patients with congenital blood coagulation factor XIII A-subunit deficiency has been demonstrated, and that its safety is acceptable in view of its observed benefits. Since the number of subjects enrolled in the clinical studies is limited, further data on the safety and efficacy of catridecacog in the target population should be accumulated in post-marketing surveillance.

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

[Indication]

Control of bleeding tendency in patients with congenital blood coagulation factor XIII A-subunit deficiency

[Dosage and administration]

The product should be reconstituted with the entire volume of the supplied solvent, and then be administered as a slow intravenous injection at a rate of  $\leq 2$  mL/min.

The recommended dosage of catridecacog for routine prophylaxis is 35 IU/kg body weight every 4 weeks.

A single dose of catridecacog 35 IU/kg body weight may be administered for on-demand treatment of bleeding.

[Conditions for approval]

The applicant is required to:

- Develop and appropriately implement a risk management plan.
- Conduct a use-results survey that should cover all Japanese patients receiving the product, to identify the characteristics of patients receiving the product, to collect efficacy and safety data, and to take appropriate measures to ensure the proper use of the product, wherever possible, since

the number of subjects enrolled in the Japanese clinical studies of the product is extremely limited.  
The survey should be continued for a certain period of time.

## Review Report (1)

January 19, 2015

### I. Product submitted for registration

[Brand name]	NovoThirteen 2500 IU for Intravenous Injection
[Non-proprietary name]	Catridecacog (Genetical Recombination)
[Applicant]	Novo Nordisk Pharma Ltd.
[Date of application]	August 29, 2014
[Dosage form/Strength]	Lyophilized powder for solution for injection: One vial contains 2500 IU of Catridecacog (Genetical Recombination) to be reconstituted prior to administration.
[Proposed indication]	Control of bleeding tendency in patients with congenital blood coagulation factor XIII A-subunit deficiency

#### [Proposed dosage and administration]

The product should be reconstituted with the entire volume of the supplied solvent, and then be administered as a slow intravenous injection at a rate of  $\leq 2$  mL/min. The usual dosage of catridecacog is 35 IU/kg body weight once a month, but the dose should be adjusted appropriately according to the bleeding condition of the patient.

If a bleeding episode requiring treatment occurs during prophylactic treatment with the product, an additional dose of 35 IU/kg body weight should be administered. The dose should be adjusted and additional doses should be considered as appropriate according to the patient's clinical symptoms.

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

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

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

Blood coagulation factor XIII (FXIII), a pro-transglutaminase, is the final enzyme in the blood coagulation cascade. In plasma, FXIII circulates as a non-covalent heterotetramer composed of two FXIII A-subunits and two FXIII B-subunits (FXIII A<sub>2</sub>B<sub>2</sub>). When the protein FXIII is cleaved by thrombin, the FXIII A-subunit dissociates from its carrier FXIII B-subunit and thereby the active site of the FXIII enzyme is exposed. The FXIII B-subunit is present in excess in the plasma, and a certain percentage of the FXIII B-subunit occurs as free form (*Blood*. 1988;72:1645-50).

Congenital FXIII deficiency is a bleeding disorder caused by either a quantitative decrease or qualitative abnormality of FXIII, and may be accompanied with serious hemorrhagic symptoms. The number of Japanese patients with congenital FXIII deficiency has been reported to be 67 (Japan Foundation for AIDS Prevention. *The 2013 annual report on the MHLW-sponsored nationwide survey on coagulopathy*. 2014) or 52 (Blood Products Research Organization. *The Blood Products Research Organization Newsletter*. 2013;138). Congenital FXIII deficiency is caused by either FXIII A-subunit or FXIII B-subunit deficiency. A vast majority of patients ( $\geq 95\%$ ) with congenital FXIII deficiency are considered to have deficiency of the FXIII A-subunit that contains the active site of the enzyme (*Thromb Haemost*. 2007;97:914-21).

The basic treatment for patients with congenital FXIII subunit-A deficiency is to administer FXIII at adequate doses to achieve hemostasis. FXIII may also be administered regularly to prevent bleeding episodes (*Haemophilia*. 2004;10:593-628, *Haemophilia*. 2008;14:1190-200, *Br J Haematol*. 1999;107:468-84, *Semin Thromb Hemost*. 1996;22:419-25, *Semin Thromb Hemost*. 2009;35:426-38). Currently in Japan, a human plasma-derived FXIII product (Fibrogammin P I.V. Injection, marketed by CSL Behring K.K.) has been approved.

Catridecacog (Genetical Recombination) (hereinafter referred to as "catridecacog") is a recombinant protein developed by ZymoGenetics and Novo Nordisk, which composes two FXIII A-subunits.

During the clinical development of catridecacog, a foreign phase I study in healthy subjects was initiated in January 2003 (Study F13-1661), and a foreign phase III study in patients with congenital FXIII A-subunit deficiency was initiated in 11 countries in August 2008 (Study F13CD-1725). In September 2009, a multi-regional phase III study in patients with congenital FXIII A-subunit deficiency started in 12 countries including Japan (Study F13CD-3720).

Catridecacog was approved in Canada in 2012, and has been approved in 8 countries or regions, including Europe and the United States, as of August 2014.

## **2. Data relating to quality**

### **2.A Summary of the submitted data**

#### **2.A.(1) Drug substance**

The drug substance is prepared by adding sucrose, polysorbate 20, and L-histidine to the active ingredient catridecacog.

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

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

The expression construct for blood coagulation factor XIII (FXIII) A-subunit was prepared by inserting an FXIII A-subunit gene isolated from a human placental tissue cDNA library into an expression vector using recombinant technology. *Saccharomyces cerevisiae* was transformed with the obtained FXIII A-subunit expression construct, and a clone expressing the FXIII A-subunit gene was isolated. The clone was used to generate the master cell bank (MCB) and working cell bank (WCB).

#### **(b) Control of cell banks**

The MCB, WCB, end-of-production cells (EPC; WCB cells at the limit of *in vitro* cell age used for production), and late-expanded cells (LEC; EPC cells further cultured under pilot scale conditions beyond the limit of *in vitro* cell age used for production), were subjected to characterization (i.e., cell viability, plasmid carriage rate, identification of the target protein [Western blot analysis], identification of plasmid DNA fragment [Southern blot analysis], phenotypes on selective media, marker gene identification [Southern blot analysis], DNA sequencing, determination of plasmid copy number, and identification of the cells). The cell banking system was confirmed to be genetically stable. No adventitious microbial agents were detected in microbial purity tests.

Stability testing was conducted for the MCB and WCB, and appropriate storage conditions have been established. While new WCBs may be generated as needed, there are no plans to prepare a new MCB.

### **2.A.(1.2) Manufacturing process**

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

Process validation of the commercial-scale production processes for the drug substance has revealed that all processes are adequately controlled.



**Table 2-1. Manufacturing process for the drug substance**

Process	Intermediates/drug substance	In-process control tests
<b>Fermentation</b>		
Inoculation and expansion of the culture		Biomass analysis, contamination test for the inoculation source/culture samples
Main fermentation		Tests for contamination of the culture medium, contamination test for the inoculation source/culture samples, dry weight of cells, exhaust gas analysis, percentage of colonies not containing the plasmid, and identification of the plasmid DNA fragment using Southern blot analysis
<b>Recovery</b>		
Homogenization		
Clarification		
[REDACTED]	Eluate	Content, yield, viable cell count, endotoxin
<b>Purification</b>		
[REDACTED]	Eluate	Content, yield, host cell proteins, purity, viable cell count, endotoxin
[REDACTED]	Eluate	[REDACTED]
[REDACTED]	Eluate	Content, yield, host cell proteins, purity, viable cell count, endotoxin
[REDACTED]	Condensate	Yield
•Preparation, filtration and storage of the drug substance	Drug substance (stored at [REDACTED] ± [REDACTED] °C)	Filter integrity test

Critical steps are indicated with gray shading.

**2.A.(1).3 Manufacturing process development (comparability)**

The major changes in the manufacturing process during the development of the drug substance are described below. When the manufacturing process was changed from Process A to B and from Process D to E, the manufacturing site was changed.

- [REDACTED]
- [REDACTED]
- Change from Manufacturing Process C to D: Changes in fermentation scale and the sterilization method for the medium.

- [REDACTED]
- [REDACTED]

The drug substance was confirmed to be comparable in terms of quality attributes before and after these manufacturing process changes. At the time of changing from Manufacturing Process D to E, studies on comparability of quality attributes and bioequivalence were carried out in healthy subjects [see "4.(i) Summary of biopharmaceutic studies and associated analytical methods"].

## **2.A.(1).4 Characterization**

### **(a) Structure/Composition**

#### **i) Primary structure**

- The results of amino acid composition analysis indicate that the amino acid composition of catridecacog is consistent with the theoretical composition predicted by the DNA sequence. The results of peptide mapping using endopeptidase Lys-C (Lys-C peptide mapping) were consistent with the theoretical sequence expected from the DNA sequence.
- In N-terminal amino acid sequencing using Edman degradation, no amino acid was detected, suggesting the acetylation of the serine residue in the N-terminal position as reported for the FXIII A-subunit derived from human plasma (*Biochemistry*. 1986;25:6900-6, *Proc Natl Acad Sci*. 1986;83:8019-23).

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

- The results of cysteine mapping using 4-vinylpyridine indicate that all 9 cysteine residues of FXIII A-subunit are in the free form. No disulfide bonds were identified; this is a finding consistent with a report on the FXIII A-subunit derived from human plasma (*J Biol Chem*. 1974;249:940-50).
- As circular dichroism spectroscopy revealed a spectrum typical of an alpha-helix in the far ultraviolet region (190-260 nm), the drug substance was confirmed to have an alpha-helix structure.
- An analysis by size exclusion high performance liquid chromatography (SE-HPLC) indicated that catridecacog binds to the FXIII B-subunit derived from human plasma to form a heterotetramer (FXIII A<sub>2</sub>B<sub>2</sub>).

#### **iii) Post-translational modification**

- The results of mass spectrometry and Lys-C peptide mapping did not indicate the presence of N- or O-linked oligosaccharide chains; this is a finding consistent with reports on the FXIII A-subunit derived from human plasma (*Biochemistry*. 1986;25:6900-6, *Proc Natl Acad Sci*. 1986;83:8019-

23). No other post-translational modifications such as phosphorylation were detected by analyses including mass spectrometry.

### **(b) Physicochemical properties**

#### i) Molecular weight

- The results of mass spectrometry were consistent with the theoretical value predicted from the amino acid sequence.
- Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) revealed a band of 83 kDa corresponding to a monomer.
- Native polyacrylamide gel electrophoresis (Native-PAGE) under a non-denaturing condition revealed a band of 166 kDa corresponding to a dimer.

#### ii) Liquid Chromatography

- [REDACTED]
- [REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED] Since the specific activity and the results of peptide map for peak [REDACTED] and peak [REDACTED] were equivalent to those of peak [REDACTED], they were considered product-related substances.
- [REDACTED]  
[REDACTED]

#### iii) Spectroscopic profiles

- The ultraviolet absorption spectrum of the drug substance showed a specific absorbance maximum at approximately 280 nm with no absorbance at wavelengths  $\geq 310$  nm. This indicates that the drug substance is a highly purified protein. The mean molar absorptivity of the drug substance was  $128 \times 10^3 \text{ mol}^{-1}\text{L}\cdot\text{cm}^{-1}$ .
- In the fluorescence spectrum at 380 nm excitation wavelength in the presence of 1-anilino-8-naphthalenesulfonate (ANS), the fluorescence maximum wavelength was approximately 495 nm.

#### iv) Others

- Isoelectric focusing revealed multiple bands around the isoelectric point of the drug substance. (pI was approximately pH 5.9.) These multiple bands were considered to be derived from product-related substances detected by IE-HPLC.
- Solubility testing revealed that the drug substance is freely soluble in pH 7 to 10 and slightly soluble in pH 3 to 6.

**(c) Biological properties**

- In a clot solubility test, fibrin clot lysis time was prolonged depending on the concentration of catridecacog.
- In a transglutaminase activity assay,  $k_{cat}/K_m$  value ranged from 7.2 to  $8.3 \times 10^3 \text{ mol}^{-1}\text{L}\cdot\text{sec}^{-1}$ .
- Berichrom assay, a synthetic substrate assay using human FXIII deficient plasma and thrombin, was conducted to assess potency and catridecacog was confirmed to have a FXIII activity.

[REDACTED]

**(d) Product-related substances**

[REDACTED]

**(e) Impurities**

i) Process-related impurities

[REDACTED]

All of the process-related impurities have been shown to be consistently removed in the manufacturing process. Host cell protein (HCP) is controlled by the specifications set for the drug substance.

ii) Product-related impurities

[REDACTED]

These product-related impurities are controlled by the specifications for the drug substance. Non-proteolytically activated catridecacog (rFXIIIa<sup>o</sup>) is an enzymatically active molecular variant reported to be generated without releasing activated peptide under particular conditions such as high salt concentration, in contrast to the proteolytically activated catridecacog made by releasing 37-amino acid activation peptide through thrombin activation (*Biochem. J.* 1990;267:557-60). The potency of rFXIIIa<sup>o</sup> was determined with a synthetic substrate assay in the absence of thrombin (rFXIIIa<sup>o</sup> assay). None of the proteolytically activated, oxidized or deamidated catridecacog was found in the drug substance.

**2.A.(1).5 Management of the drug substance**

[REDACTED]

### 2.A.(1).6) Stability of the drug substance

Primary stability studies on the drug substance are shown in Table 2-2.

**Table 2-2. Overview of primary stability studies on the drug substance**

Study	Manufacturing Process	No. of batches	Storage condition	Storage package	Storage period
Long-term	Manufacturing Process █	3	█ ± █ °C	low-density polyethylene package	█ months
	Manufacturing Process F	6			█ months or █ months* <sup>1</sup>
Accelerated (1)	Manufacturing Process █	3	█ ± █ °C		3 months
Accelerated (2)	Manufacturing Process █	3	█ ± █ °C		6 weeks

\*<sup>1</sup> The study will be continued up to 48 months.

Although a slight increase in FXIIIa<sup>o</sup> was observed in the long-term studies, the drug substance met all specifications throughout the study period. No changes were observed in the accelerated testing (1). In the accelerated testing (2), a decrease in purity and an increase in rFXIIIa<sup>o</sup> were observed.

█  
 █  
 █  
 █  
 █  
 █  
 █

Forced degradation studies were conducted under various conditions, i.e., high temperature, oxidation, acid/alkaline conditions, and light (1,500,000 lux·hr) and mechanical stress (rotation). The results indicated that the drug substance is susceptible to degradation via heat, oxidation, alkaline condition, and light. Since the drug substance was precipitated in acid, the results under acidic condition were not obtained.

Based on the above, a shelf-life of █ months was established for the drug substance when stored in low-density polyethylene containers at █ ± █ °C.

### 2.A.(2) Drug Product

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

The drug product is a lyophilized powder for solution for injection containing 2500 IU of the active ingredient in 1 vial. The drug product contains L-histidine, sodium chloride, sucrose, and polysorbate

20 as excipients. Vials are overfilled to compensate for liquid loss during preparation and ensure the labeled amount. The secondary package is a paper carton.

The drug product is provided with a glass vial containing 3.2 mL of Water for Injection (JP).

#### **2.A.(2).2 Manufacturing process**

The drug product manufacturing process comprises thawing of the drug substance, preparation of the excipient solution, mixing, pH adjustment, final mixing, sterile filtration, filling, lyophilization, and rubber stoppering and cap sealing of vials, as well as packaging, labeling, and storage. [REDACTED]

[REDACTED] The manufacturing process for the drug product was subjected to a process validation in the scale of commercial production; the process was found to be controlled adequately.

#### **2.A.(2).3 Manufacturing process development**

The major changes in the manufacturing process during the pharmaceutical development are described below.

- From Process A to B: Changes in composition of the finished product, vial size, and lyophilization process.
- From Process B to C (proposed process): Changes in composition and filling content of the finished product, and lyophilization process.

The comparability of the quality attributes between pre-change and post-change drug products has been confirmed accordingly with the above change in manufacturing process.

#### **2.A.(2).4 Control of drug products**

[REDACTED]

#### **2.A.(2).5 Stability of drug product**

Primary stability studies on the drug product are as shown in Table 2-3.

**Table 2-3. Overview of primary stability studies on the drug product\*1**

Study	Manufacturing process	No. of batches	Storage condition	Storage form	Storage period
Long-term	Process █	3	5 ± 3°C	Glass vial	36 months
	Process F	4			█-█ months*2
Accelerated	Process █	3	25 ± 2°C, 60 ± 5% RH		6 months
	Process F	1			
In-use stability (1)	Process █	3	5°C*3		48 hours after reconstitution
	Process F	1			
In-use stability (2)	Process █	2	30°C*4		24 hours after reconstitution
	Process F	1			
Photostability	Process █	1	17.1-21.0°C, an overall illumination of ≥1.2 ×10 <sup>6</sup> lux·hr, and an integrated near ultraviolet energy of 250 W·h/m <sup>2</sup>		27 hours
			20.6-21.7°C, an overall illumination of ≥1.2 ×10 <sup>6</sup> lux·hr, and an integrated near ultraviolet energy of 250 W·h/m <sup>2</sup>		Secondary packaging 27 hours

\*1 The proposed process (Process C) was used to formulate the drug product.

\*2 One batch each was stored for █ months, █ months, █ months, or █ months.

\*3 Samples stored for 0, 4, 7, 9, or 24 months at 5 ± 3°C were used.

\*4 Samples stored for 3, 24, or 36 months at 5 ± 3°C were used.

Although a slight increase in rFXIIIa° was observed in the long-term studies, the drug product met all specifications throughout the study period. In the accelerated testing, an increase in rFXIIIa° was observed. In the in-use stability study, no changes were observed up to 48 hours at 5°C and 6 hours at 30°C, but after storage for 24 hours at 30°C, a slight increase in rFXIIIa° was observed. In the photostability study, the increase in rFXIIIa° was higher in the drug product without secondary packaging, which protect the drug product from light, than in the drug product with it.

█  
 █  
 █  
 █  
 █  
 █  
 █  
 █  
 █

Based on the above, a shelf-life of 24 months was established for the drug product in a glass vial when stored at 2°C to 8°C under protection from light. The reconstituted solution was considered stable for 24 hours at 2°C to 8°C and for 3 hours at ≤30°C.

**2.A.(3) Reference standards or reference materials**

The primary reference material (PRM) and secondary reference material (SRM) are prepared from the drug substance and stored at ≤-70°C. Specifications and test methods are defined for the reference

materials. Qualification of the reference materials is checked regularly. The potency of the PRM is determined using the World Health Organization (WHO) International Standard FXIII Plasma.

## **2.B Outline of the review by PMDA**

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

## **3. Non-clinical data**

The applicant stated that the 1 mg of catridecacog is equivalent to approximately 167 IU on the basis of the finding that the specific activity (FXIII activity of 1 mg of the protein) of the reference material prepared from the drug substance was 167 IU.

### **3.(i) Summary of pharmacology studies**

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

The applicant submitted the results of primary pharmacodynamic studies (studies on [1] binding to the endogenous FXIII B-subunit, [2] fibrin cross-linking, [3] fibrinogen cross-linking, [4] resistance against clot lysis, [5] cross-linking of plasma proteins in cynomolgus monkeys, and [6] antifibrinolytic activity on tissue plasminogen activator [t-PA]-induced clot lysis in a rabbit model), the results of secondary pharmacodynamic studies (a study on the binding of catridecacog with various human blood cells and a study of the effect of catridecacog on clot formation in rabbits) and the results of safety pharmacology studies (studies using cynomolgus monkeys).

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

##### ***In vitro* studies**

The applicant submitted the results of *in vitro* primary pharmacodynamic studies, as summarized in 3.(i).A.(1).1) to 4).

##### **3.(i).A.(1).1 Binding to the endogenous FXIII B-subunit (4.2.1.1-1, RES-FXIII-0025)**

Mouse, rat, rabbit, dog, monkey, and human serum samples were incubated with untreated resin (negative control) or catridecacog-bound resin. Proteins bound to the resin were separated by using SDS-PAGE, and were stained with Coomassie dye. Only catridecacog-bound resin showed a band at almost the same position corresponding to the molecular weight of the human FXIII B-subunit run with the samples. N-terminal sequencing revealed that the band was identified as FXIII B-subunit.

Based on the above results, the applicant explained that catridecacog forms complexes with the endogenous FXIII B-subunit in a variety of animal species including humans.



### **3.(i).A.(1).2 Fibrin cross-linking (4.2.1.1-2, RES-FXIII-0024)**

Catridecacog was added at concentrations from 0 to 20 µg/mL to FXIII deficient human plasma, and cynomolgus monkey plasma in which FXIII was depleted with rabbit anti-catridecacog antibodies. The mixtures were incubated with thrombin and CaCl<sub>2</sub>, to confirm the cross-linking of fibrin in the samples by SDS-PAGE and Coomassie staining. As a result, only the plasma samples added with catridecacog showed a band at the position corresponding to the molecular weight of fibrin-gamma chain dimer in the standard protein, and the band density tended to increase as the concentration of catridecacog increased.

Based on the above results, the applicant explained that catridecacog is able to cross-link fibrin.

### **3.(i).A.(1).3 Fibrinogen cross-linking by thrombin-activated catridecacog (activated catridecacog) and non-activated catridecacog (4.2.1.1-3, RES-FXIII-0063)**

#### **(a) Experiment using thrombin-activated catridecacog**

Activated catridecacog was added to heparinized human and cynomolgus monkey plasma samples at concentrations of 0, 2, 5, 10, 15, 20, 30, 40, or 50 µg/mL. The mixtures were incubated to confirm the cross-linking of fibrinogen in the samples by SDS-PAGE and Coomassie staining. Plasma samples containing activated catridecacog at concentrations of ≥15 µg/mL showed a band at the same position corresponding to the molecular weight of fibrin gamma-chain dimer in the reference protein.

Based on the above results, the applicant explained that activated catridecacog is able to cross-link fibrinogen.

#### **(b) Experiment using catridecacog not activated by thrombin**

Catridecacog was added to heparinized human plasma at concentrations of 0, 20, 100, 200, 400, or 800 µg/mL. The mixtures were incubated to confirm the cross-linking of fibrinogen in the samples by SDS-PAGE and Coomassie staining. Plasma samples containing catridecacog at concentrations of ≥400 µg/mL showed a band at the same position corresponding to the molecular weight of fibrin gamma-chain dimer in the reference protein.

Based on the above results, the applicant explained that even catridecacog not activated by thrombin is able to crosslink fibrinogen at high concentrations (≥400 µg/mL).

### **3.(i).A.(1).4 Resistance against clot lysis (4.2.1.1-4, LCP051125)**

Catridecacog was added at concentrations of 0, 2.5, 5.0, 10, 20, or 40 µg/mL to FXIII-deficient human plasma containing activated recombinant blood coagulation factor VII, and a buffer containing tissue factor, CaCl<sub>2</sub>, t-PA, and phospholipid vesicles was added to prepare samples. The process of coagulation and fibrinolysis of these samples was observed using turbidity as an indicator. The time from the beginning of the reaction to half-maximum turbidity of the sample (coagulation time) was not affected

by the concentration of catridecacog. However, the time from the half-maximum turbidity to the maximum turbidity and then back to the half-maximum turbidity (clot lysis time) was prolonged as the concentration of catridecacog increased (Table 3-1).

**Table 3-1. Coagulation time and clot lysis time in human plasma**

Catridecacog concentration (µg/mL)	0	2.5	5.0	10	20	40
Coagulation time (sec)	787	796	815	834	806	796
Clot lysis time (sec)	2251	3015	3631	6920	9423	11,755

Table 3-2 shows the clot lysis time in a similar study in the presence of potato tuber carboxypeptidase inhibitor (PTCI), an inhibitor of thrombin-activatable fibrinolysis inhibitor (TAFI).

**Table 3-2. Clot lysis time in human plasma with and without PTCI**

Catridecacog concentration (µg/mL)	0	2.5	5.0	10	20	40	
Clot lysis time (sec)	With PTCI	1111	1432	1654	1873	1877	1979
	Without PTCI	1090	1711	2838	3722	4785	6037

Based on the above results, the applicant explained that catridecacog acts mainly as an anti-fibrinolytic agent, and enhances the anti-fibrinolytic activity of TAFI.

### ***In vivo* studies**

The applicant submitted the results of *in vivo* primary pharmacodynamic studies, as summarized in 3.(i).A.(1).5) to 6).

#### **3.(i).A.(1).5) Plasma protein cross-linking (4.2.1.1-6, RES-FXIII-0058)**

Catridecacog was administered intravenously to cynomolgus monkeys (n = 1 or 2/male or female/group) at doses from 0 to 30.0 µg/mL. Plasma samples obtained from the animals were analyzed for plasma protein cross-linking by SDS-PAGE and Coomassie staining (and silver staining). The band density of cross-linked protein complexes of high molecular weight and fibrinogen gamma chain dimer increased as catridecacog dose increased.

Based on the above results, the applicant explained that catridecacog is able to cross-link plasma proteins *in vivo*.

#### **3.(i).A.(1).6) Antifibrinolytic activity on t-PA-induced clot lysis in a rabbit model (4.2.1.1-7, RES-10352)**

Catridecacog 0.4 mg/kg or saline (negative control) was administered to rabbits (n = 6 females/group), and then, their ears were cut. The cut wound was left open for 15 minutes to allow clot formation, and then t-PA was administered intravenously. The time to rebleeding from the wound (time to lysis [TTL]) was measured. No statistically significant difference in TTL was observed between the catridecacog and

negative control groups. However, TTL tended to be longer in the catridecacog group than in the negative control group.

The applicant explained that these findings suggest that catridecacog shows resistance to clot lysis, although no statistically significant difference was observed between the catridecacog and negative control groups because the study investigated only a single dose level (0.4 mg/kg) in a limited number of animals.

### **3.(i).A.(2) Secondary pharmacodynamics**

The applicant submitted the results of secondary pharmacodynamic studies, as summarized in 3.(i).A.(2).1) to 2).

#### **3.(i).A.(2).1) Binding to human blood cells (4.2.1.2-2, RES-FXIII-0018)**

In order to assess the binding between catridecacog and human blood cells *in vitro*, blood cells isolated from human whole blood were incubated with catridecacog or activated catridecacog 1 to 20 µg/mL. Flow cytometry was performed to assess whether catridecacog or activated catridecacog binds to T cells, B cells, granulocytes, and monocytes. Neither catridecacog nor activated catridecacog bound to these cells.

A purified platelet fraction derived from human whole blood (half of the aliquots were treated with thrombin to activate platelets) was incubated with catridecacog or activated catridecacog at a concentration of 5, 10, 20, or 40 µg/mL. Following incubation, flow cytometry was performed to assess whether catridecacog or activated catridecacog binds to quiescent or activated platelets. Neither quiescent nor activated platelets bound to catridecacog, but both of them bound to activated catridecacog at concentrations of ≥5 µg/mL.

#### **3.(i).A.(2).2) Effects on clot formation in a rabbit arteriovenous-shunt model (4.2.1.3-4, RES-10351)**

In order to evaluate the facilitating effect of catridecacog on clot growth, catridecacog 0.4 mg/kg or vehicle was administered to rabbits with a surgically created arteriovenous shunt (n = 4 female/group), to determine the weight of the blood clot formed around a cotton string inserted into the shunt. The clot weight did not differ between the vehicle and catridecacog groups.

The applicant explained that these results are consistent with the finding that FXIII functions as a clot stabilizer.

### **3.(i).A.(3) Safety pharmacology**

Safety pharmacology studies of catridecacog on the central nervous system and cardiovascular system were conducted as part of repeated-dose toxicity studies of catridecacog in cynomolgus monkeys (Study

SBi-1394-175 and Study NN205255) [see "3.(iii).A.(2) Repeated toxicity studies"]. The applicant explained that no concerns about safety pharmacological effects were found in the assessment of clinical observations, body temperature, electrocardiogram (ECG), heart rate, and blood pressure in these studies.

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

PMDA asked the applicant to explain the safety pharmacological evaluation of catridecacog on the respiratory system since no safety pharmacology studies on the respiratory system were conducted.

The applicant responded as follows:

No effects on the respiratory system were found in clinical observations in the toxicity studies of catridecacog 50 to 5010 IU/kg per dose. In the toxicity study in cynomolgus monkeys, deaths possibly related to the administration of catridecacog were observed in 6 of 51 animals receiving catridecacog at doses higher than the clinical dose ( $\geq 1670$  IU/kg). However, since histopathological examination of the dead animals revealed systemic clot formation and ischemic necrosis, these deaths were considered to be caused by blood coagulation from an excessive pharmacological action of catridecacog; this suggests no specific effects of catridecacog on the respiratory system. Moreover, the results of characterization indicate that catridecacog and the endogenous FXIII A-subunit are extremely similar in structure [see "2.A.(1).4 Characterization"], and the results of the primary pharmacodynamics studies indicate that catridecacog has pharmacodynamic characteristics similar to those reported for the endogenous FXIII in literature (*Thromb Res.* 1999;94:271-305, *Cardiovasc Hematol Agents Med Chem.* 2008;6:190-205, *Hemostasis and Thrombosis: Basic Principles and Clinical Practice 5th ed.* Lippincott Williams & Wilkins, 2006). Therefore catridecacog, as well as the endogenous FXIII, is not considered to affect the respiratory system. The results of the clinical studies of catridecacog do not suggest its effect on the respiratory system.

PMDA considers as follows:

The results of primary pharmacodynamics studies suggest that catridecacog functions as FXIII and can be expected to cross-link fibrin and inhibit fibrinolysis in the living body with FXIII A-subunit deficiency. The results of safety pharmacology studies and toxicity studies indicate no specific safety concerns including the effect on the respiratory system.

### **3.(ii) Summary of pharmacokinetic studies**

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

The applicant submitted pharmacokinetics data, consisting mainly of the results of studies in rats and cynomolgus monkeys, as summarized in 3.(ii).A.(1) to (4).

In these studies, enzyme-linked immunosorbent assay (ELISA) was used to determine the following: (1) total plasma concentration of free catridecacog plus heterotetramers composed of A-subunit (either endogenous A-subunit or catridecacog) and endogenous B-subunit (hereafter, "total FXIII A<sub>2</sub>

concentration"); (2) plasma concentration of heterotetramers composed of A-subunit (either endogenous A-subunit or catridecacog) and endogenous B-subunit (hereafter, "FXIII A<sub>2</sub>B<sub>2</sub> concentration"); and (3) plasma concentration of free FXIII B-subunit. Plasma FXIII activity was determined using Berichrom assay. ELISA was used to determine the amount of anti-catridecacog antibodies in plasma of rats and cynomolgus monkeys. Solid scintillation counter and quantitative whole-body autoradiography were used to determine tissue radioactivity in cynomolgus monkeys treated with <sup>125</sup>I-labeled catridecacog (hereafter, "<sup>125</sup>I-rFXIII"). Unless otherwise specified, values are expressed in mean ± standard deviation.

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

#### **Single-dose studies (4.2.2.2-1, SBi-1224-175; 4.2.2.2-2, SBi-1241-175; 4.2.2.2-3, NN207399; 4.2.2.2-4, 7333-101\_A)**

In Study SBi-1224-175, cynomolgus monkeys (n = 2/sex/group) received a single intravenous administration of catridecacog 1 or 5 mg/kg, to measure total FXIII A<sub>2</sub> concentration, FXIII A<sub>2</sub>B<sub>2</sub> concentration, and free FXIII B-subunit concentration in plasma at baseline and at 10 time points between 0.25 to 336 hours post-dose. In Study SBi-1241-175, cynomolgus monkeys (n = 4/sex/group) received a single intravenous administration of catridecacog 0.5, 1, or 5 mg/kg, to measure the total FXIII A<sub>2</sub> concentration, FXIII A<sub>2</sub>B<sub>2</sub> concentration, and free FXIII B-subunit concentration in plasma at baseline and at 12 time points from 0.25 to 672 hours post-dose. Pharmacokinetic parameters were calculated based on the total FXIII A<sub>2</sub>, FXIII A<sub>2</sub>B<sub>2</sub>, and free FXIII B-subunit concentrations (Table 3-3).

The evaluation of pharmacokinetic linearity of these substances using pharmacokinetic parameters obtained in the above showed that the clearance of total FXIII A<sub>2</sub> increased as the dose of catridecacog increased, while the area under the plasma activity/concentration-time curve from zero to infinity (AUC<sub>0-∞</sub>) of total FXIII A<sub>2</sub> did not increase in proportion to dose. The AUC<sub>0-∞</sub> of FXIII A<sub>2</sub>B<sub>2</sub> also did not increase in proportion to the dose.

The applicant discussed the above findings as follows:

It has been reported that FXIII B-subunits are present in excess in plasma compared with FXIII A-subunits, and some FXIII B-subunits are present in the free form (*Blood*. 1988;72:1645-50), and that the elimination half-life of FXIII A-subunits is prolonged when FXIII A-subunits bind to FXIII B-subunits to form a heterotetramer (*Biochem J*. 1990;267: 557-60). In Study SBi-1224-175, free FXIII B-subunit concentration decreased below the lower limit of quantification immediately after the administration of catridecacog (Table 3-3). This was considered to reflect the depletion of free FXIII B-subunits in plasma as a result of excess FXIII A-subunits after administration, which resulted in an increase in the proportion of free FXIII A-subunits with a shorter half-life. This increase in free FXIII A-subunit was considered the cause of the absence of dose-proportional increase in the AUC<sub>0-∞</sub> of total FXIII A<sub>2</sub>.

**Table 3-3. Pharmacokinetic parameters in cynomolgus monkeys**

Study Identifier	Dose (mg/kg)	Total FXIII A <sub>2</sub>		FXIII A <sub>2</sub> B <sub>2</sub>	Free FXIII B subunit	
		AUC <sub>0-∞</sub> (μg·h/mL)	CL (mL/h/kg)	AUC <sub>0-∞</sub> (μg·h/mL)	C <sub>pre-dose</sub> (μg/mL)	C <sub>0</sub> (μg/mL)
SBI-1224-175	1 (N = 4)	1620 ± 1186	0.83 ± 0.42	8729 ± 9534	1.03 ± 0.48	LTR
	5 (N = 4)	3853 ± 729	1.34 ± 0.27	13,971 ± 2564	1.36 ± 0.18	LTR
SBI-1241-175	0.5 (N = 8)	656 ± 201	0.87 ± 0.41	3239 ± 343	0.97 ± 0.26	LTR
	1 (N = 8)	985 ± 400	1.15 ± 0.42	4382 ± 1993	1.06 ± 0.48	LTR
	5 (N = 8)	2677 ± 781	1.98 ± 0.43	10,512 ± 5090	1.16 ± 0.61	LTR

N = number of animals; AUC<sub>0-∞</sub> = area under the plasma activity/concentration-time curve from zero to infinity; CL = clearance; C<sub>pre-dose</sub> = baseline plasma concentration; C<sub>0</sub> = initial concentration (plasma concentration immediately after administration); LTR = below quantification limit.

Cynomolgus monkeys (n = 1/sex/group) received a single intravenous administration of catridecacog (including <sup>125</sup>I-labelled catridecacog) at the dose of 0.5 or 5.0 mg/kg, to determine radioactivity concentrations in plasma at baseline and at 10 time points between 0.25 to 168 hours post-dose.

A comparison of the pharmacokinetics of total <sup>125</sup>I-rFXIII A<sub>2</sub> and free <sup>125</sup>I-rFXIII A<sub>2</sub> isolated using size exclusion high performance liquid chromatography revealed that the elimination half-life of free <sup>125</sup>I-rFXIII A<sub>2</sub> (4.8 ± 0.3 hours at 0.5 mg/kg, and 3.6 ± 0.6 hours at 5.0 mg/kg) was shorter than that of total <sup>125</sup>I-rFXIII A<sub>2</sub> (89 ± 11 hours at 0.5 mg/kg, and 118 ± 35 hours at 5.0 mg/kg). The applicant explained that these findings indicate a short plasma elimination half-life of free catridecacog.

The initial plasma concentration (C<sub>0</sub>) of total <sup>125</sup>I-rFXIII A<sub>2</sub> was 9.8 ± 0.8 and 92.9 ± 3.8 μg/mL at the doses of 0.5 and 5.0 mg/kg, respectively, showing a dose-proportional (10-fold) increase. On the other hand, the initial plasma concentration (C<sub>0</sub>) of free <sup>125</sup>I-rFXIII A<sub>2</sub> was 5.8 ± 1.3 and 101.9 ± 10.1 μg/mL at the doses of 0.5 and 5.0 mg/kg, respectively, showing that the C<sub>0</sub> increased more than proportionally to the dose.

The applicant discussed the cause of the more than dose-proportional increase in C<sub>0</sub> of free <sup>125</sup>I-rFXIII A<sub>2</sub> as follows:

At the dose of 0.5 mg/kg, most of <sup>125</sup>I-rFXIII A<sub>2</sub> is considered to be bound to free FXIII B-subunits. Thus, the proportion of free <sup>125</sup>I-rFXIII A<sub>2</sub> may become small. On the other hand, at the dose of 5.0 mg/kg, the amount of free FXIII B-subunits is smaller than that necessary to bind to all catridecacog molecules, and thus the proportion of <sup>125</sup>I-rFXIII A<sub>2</sub> is considered to become larger than that observed at 0.5 mg/kg.

Young cynomolgus monkeys aged from 46 to 60 weeks and matured cynomolgus monkeys aged from 149 to 223 weeks received a single intravenous administration of catridecacog 1 mg/kg (n = 3/sex/group), to determine FXIII activity at baseline and at 13 time points between 0.25 to 504 hours post-dose.

A comparison of the pharmacokinetics of catridecacog in young and matured cynomolgus monkeys revealed that baseline FXIII activity did not differ between young and matured animals (1.11-1.81 IU/mL and 1.25-1.42 IU/mL, respectively), while the AUC from 0 to 240 hours ( $AUC_{0-240h}$ ) was  $115 \pm 46$  IU·h/mL in young animals and  $221 \pm 32$  IU·h/mL in matured animals. The exposure to catridecacog was lower in young animals than in matured animals.

The applicant explained that the cause of this finding was not identified and whether the recommended dose should be adjusted by age would be investigated in clinical pharmacology studies [see "4.(ii).A.(3).4 Foreign phase III clinical study"].

### **3.(ii).A.(2) Distribution (4.2.2.3-1, 7333-101\_B)**

Cynomolgus monkeys (n = 2/sex/group) received a single intravenous administration of  $^{125}I$ -rFXIII at 0.5 or 5.0 mg/kg, to determine radioactivity distribution in plasma and tissues at 2 and 72 hours post-dose. At 2 and 72 hours post-dose, radioactivity is mainly distributed in the plasma and vascular-rich organs (e.g., the liver, kidney, and lung). No tissues, except for the thyroid, as could be expected due to the iodine label, were exposed to radioactivity at tissue to plasma ratios above 1 at either 2 or 72 hours post-dose. Radioactivity concentration at 72 hours post-dose was lower than that at 2 hours post-dose in all tissues other than the thyroid.

Based on these findings, the applicant discussed that catridecacog is not accumulated in tissues.

### **3.(ii).A.(3) Metabolism**

No studies on metabolism have been conducted.

### **3.(ii).A.(4) Excretion (4.2.2.3-1, 7333-101\_B)**

Cynomolgus monkeys (n = 1/sex/group) received a single intravenous administration of  $^{125}I$ -rFXIII at 0.5 or 5.0 mg/kg, to determine radioactivity in urine and feces collected up to 168 hours post-dose. Urine and feces accounted for 51.5% and 1.93% of the administered radioactive dose, respectively, in the 0.5 mg/kg group, and 41.8% and 2.37%, respectively, in the 5.0 mg/kg group. Urine was considered the predominant route of excretion.

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

Since the applicant did not use disease models such as cynomolgus monkey models of FXIII deficiency, no data on the pharmacokinetics of catridecacog in animals with FXIII deficiency have been obtained.

PMDA considers that the submitted results of pharmacokinetic studies of catridecacog are consistent with the findings on the disposition of endogenous FXIII A-subunit, which suggests that the pharmacokinetic profile of catridecacog is similar to the disposition of endogenous FXIII A-subunit.

Since catridecacog is a protein product, its metabolism was not investigated in animals on the basis of the "Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals" (PFSB/ELD Notification No. 0323-1 dated March 23, 2012; ICH-S6(R1)). This is acceptable.

### **3.(iii) Summary of toxicology studies**

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

The applicant submitted toxicity data of catridecacog, i.e., the results of single-dose toxicity studies, repeated-dose toxicity studies, and local tolerance studies. Cynomolgus monkeys were used in main single-dose and repeated-dose toxicity studies, because catridecacog exerts its pharmacological activity in this animal species and because the levels of blood coagulation/fibrinolytic factors and blood coagulation parameters (prothrombin time, activated partial thromboplastin time, and thrombin time) in cynomolgus monkeys are more similar to humans as compared with other animals such as rodents, rabbits, dogs, and pigs (*Drug Research*. 1994;44:793-7).

#### **3.(iii).A.(1) Single-dose toxicity (4.2.3.1-1, SBi-1220-175; 4.2.3.1-2, SBi-1278-175; 4.2.3.2-4, SBi-1249-175: all are reference data)**

Single dose toxicity studies (Studies SBi-1220-175, SBi-1278-175, and SBi-1249-175) were conducted in cynomolgus monkeys given single intravenous dose of catridecacog. Deaths were observed in animals receiving catridecacog at doses  $\geq 21.9$  mg/kg (3657 IU/kg, 104-fold the clinical dose). Histopathological examination of the dead animals revealed systemic clot formation and ischemic necrosis. These deaths were thus considered to be caused by blood coagulation due to an excessive pharmacological action of catridecacog. No deaths or changes in clinical observations were found in animals after the single-dose administration  $\leq 21.2$  mg/kg (3540 IU/kg).

#### **3.(iii).A.(2) Repeated-dose toxicity**

Two-week, 4-week, and 27-week repeated-dose toxicity studies of catridecacog in cynomolgus monkeys (Studies SBi-1394-175, SBi-1266-175, and NN205255) were conducted as repeated-dose toxicity studies. In addition, a 4-week repeated-dose toxicity study in rats (Study NN209502) was conducted to compare catridecacog manufactured with Process E and that with Process D (for Processes D and E, [see "2.A.(1).3) Manufacturing process development (comparability)"]).

#### **3.(iii).A.(2).1 Two-week repeated intravenous dose toxicity studies in cynomolgus monkeys (4.2.3.2-5, SBi-1394-175)**

Catridecacog was administered intravenously at doses of 0 (vehicle), 0.3, 3, or 6 mg/kg (1002 IU/kg, 29-fold the clinical dose) once daily for 2 weeks to cynomolgus monkeys (n = 5/sex/group in the vehicle and 3 mg/kg groups; n = 3/sex/group in the 0.3 and 6 mg/kg groups). No animals in any group died. No effects of catridecacog were observed. The no observed adverse effect level (NOAEL) in this study was considered to be 6 mg/kg.



**3.(iii).A.(2).2) Four-week repeated intravenous dose toxicity studies in cynomolgus monkeys (4.2.3.2-6, SBI-1266-175)**

Catridecacog was administered intravenously at doses of 0 (vehicle), 5, 8, or 12.5 mg/kg (2088 IU/kg, 60-fold the clinical dose) every 2 weeks for 4 weeks (a total of 3 doses) to cynomolgus monkeys (n = 5/sex/group in the vehicle and 12.5 mg/kg groups; n = 3/sex/group in the 5 and 8 mg/kg groups). No animals in any group died. No effects of catridecacog were observed. The NOAEL in this study was considered to be 12.5 mg/kg.

**3.(iii).A.(2).3) Twenty-seven-week repeated intravenous dose toxicity study in cynomolgus monkeys (4.2.3.2-7, NN205255)**

Catridecacog was administered intravenously at doses of 0 (vehicle), 1, 3, or 10 mg/kg (1670 IU/kg, 48-fold the clinical dose) every 2 weeks for 27 weeks (a total of 14 doses) to cynomolgus monkeys (n = 5/sex in the vehicle group; n = 3/sex/group in the 1 and 3 mg/kg groups; n = 10/sex in the three 10 mg/kg groups). In the 10 mg/kg groups, 5 animals of each sex were sacrificed at 13 weeks to compare the effects of 13- and 27-week treatment. One animal in the 10 mg/kg groups died 4 days after the first administration. Histopathological examination of this animal revealed systemic clot formation and ischemic necrosis, suggesting that the death was caused by blood coagulation due to an excessive pharmacological action of catridecacog. In the 10 mg/kg groups, decreased weight gain was observed up to Week 4 of treatment, and transient decreases in hematocrit and reticulocyte count were observed at Weeks 7 and 13, respectively. The comparison of the effects of 13- and 27-week treatment did not reveal any differences in findings. No toxicological effects of catridecacog were observed in the 1 or 3 mg/kg groups. The NOAEL in this study was considered to be 3 mg/kg.

**3.(iii).A.(2).4) Four-week repeated intravenous dose toxicity studies in rats (4.2.3.2-2, NN209502)**

Rats (n = 15/sex/group) received catridecacog manufactured with Process E at doses of 0 (vehicle), 1, 5, or 15 mg/kg (2505 IU/kg; 72-fold the clinical dose) or catridecacog manufactured with Process D at doses of 1 or 5 mg/kg intravenously once daily for 4 weeks. No animals in any group died. Histopathological examination revealed hyperplasia of lymphoid follicles in the spleen of animals receiving 15 mg/kg catridecacog manufactured with Process E and in all animals receiving catridecacog manufactured with Process D. This finding was considered a non-specific physiological response to foreign matters such as foreign proteins rather than a change caused specifically by catridecacog. This study revealed that toxicity profile does not differ between catridecacog manufactured with Process E and that with Process D.

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

Since catridecacog is a protein product composed only of FXIII A-subunit, and there are no concerns for genotoxicity of process-related impurities, no genotoxicity studies of catridecacog have been conducted on the basis of ICH-S6(R1).

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

The structure and kinetic characteristics of catridecacog are similar to those of endogenous FXIII [see "2.A.(1).4 Characterization" and "3.(ii) Summary of pharmacokinetic studies"]. Catridecacog is to be administered to patients with FXIII A-subunit deficiency in order to supplement the FXIII A-subunit within the physiologically necessary range. Since catridecacog is considered to have a low carcinogenic potential, no carcinogenicity studies of catridecacog have been conducted, taking into account of ICH-S6 (R1).

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

No reproductive and developmental toxicity studies of catridecacog have been conducted.

### **3.(iii).A.(6) Local tolerance**

#### **3.(iii).A.(6.1) Local tolerance study in rabbits (4.2.3.6-1, NN205496)**

Rabbits (n = 4 females/group) received a single dose of catridecacog 0.35 mg/kg (58 IU/kg, 1.7-fold the clinical dose) administered intravenously or intra-arterially to the left ear (the right ear was left untreated). Mild inflammatory changes observed at the site of administration were considered to be associated with injection procedure. Local irritant effects of catridecacog in the clinical setting were considered tolerable.

#### **3.(iii).A.(6.2) Local tolerance study in rabbits (4.2.3.6-2, NN209504)**

Rabbits (n = 4 females/group) received a single dose of catridecacog 0.25 mg/kg (42 IU/kg, 1.2-fold the clinical dose) administered intravenously, intra-arterially, or perivenously to the left ear. The rabbits also received a single dose of vehicle to the right ear at the same dose via the same routes as catridecacog. Inflammatory changes at the administration site were observed in all groups. The severity of inflammation was similar for the catridecacog and vehicle groups among animals receiving intra-arterial and perivenous administration. The severity of inflammation was slightly higher in the catridecacog group than in the vehicle group among animals receiving intravenous administration. All changes were mild in severity, and local irritant effects of catridecacog in the clinical setting were considered tolerable.

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

PMDA considers that deaths observed in toxicity studies of catridecacog were caused by excessive pharmacological action, and that there are no specific problems observed in terms of systemic toxicity and local tolerance. PMDA accepted the applicant's explanation on the omission of genotoxicity and carcinogenicity studies on the basis of the ICH-S6(R1), and conducted the following review in terms of reproduction toxicity studies.

#### **3.(iii).B.(1) Omission of reproduction toxicity studies**

The applicant explained the reasons for the omission of reproduction toxicity studies as follows:

Clot formation is known as a cause of abortion or stillbirth in patients with antiphospholipid syndrome, and as a risk factor for recurrent abortion (*Nat Rev Rheumatol.* 2011;7:330-9, *Obstetrics & Gynecology.* 2007;109:1146-55). Accordingly, an overdose of catridecacog to pregnant animals with normal blood coagulation activity is expected to enhance coagulation and cause similar effects on the fetus.

As for the effects of catridecacog in pregnant women with FXIII A-subunit deficiency, FXIII replacement therapy has been reported to be beneficial in maintaining pregnancy in patients with recurrent spontaneous abortions associated with FXIII deficiency (*Blood Coagul Fibrinolysis.* 2014;25:199-205, *Placenta.* 2000;21:388-93, *Gynecol. Obstet. Invest.* 1990;29:235-8, *Blut.* 1987;55:45-8, *J. Clin Invest.* 1987;79:649-52). The molecular weight of catridecacog is 166 kDa, and umbilical cord bleeding has been reported to occur in a few hours after birth in newborns with FXIII deficiency; catridecacog is therefore unlikely to cross the placenta to affect the fetus directly. Accordingly, catridecacog is unlikely to adversely affect pregnancy or exert teratogenic effects.

PMDA considers as follows:

PMDA understands the applicant's explanation that excessive coagulation caused by an overdose of catridecacog to normal maternal animals may be associated with the risk of toxicity during ontogeny.

PMDA considers the use of catridecacog in patients with FXIII A-subunit deficiency as follows:

Approximately 30% of patients with FXIII A-subunit deficiency, if untreated, have been reported to experience intracranial hemorrhage, a major cause of death or disability in this patient population (*Br J Haematol.* 1999;107:468-84). Patients with FXIII A-subunit deficiency are thus considered to have increased health risks associated with bleeding events, and therefore some pregnant or possibly pregnant women may have no choice but to use catridecacog. Accordingly, catridecacog may be administered to pregnant or possibly pregnant women after considering the risk and benefit of the treatment, provided that healthcare professionals are appropriately instructed to use catridecacog only if the therapeutic benefits outweigh the risks.

#### **4. Clinical data**

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

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

Plasma FXIII activity was determined using Berichrom assay. ELISA was used to determine the following: total plasma concentration of free catridecacog plus heterotetramers composed of A-subunit (either endogenous A-subunit or catridecacog) and endogenous B-subunit (total FXIII A<sub>2</sub> concentration); plasma concentration of heterotetramers composed of A-subunit (either endogenous A-subunit or catridecacog) and endogenous B-subunit (FXIII A<sub>2</sub>B<sub>2</sub> concentration); and plasma concentration of free FXIII B-subunit. ELISA was also used to determine the amount of anti-catridecacog antibodies in plasma.

The applicant submitted biopharmaceutical data, i.e., the results of a bioequivalence study (Study 5.3.1.2-1: NN1841-3788) that compared 2 catridecacog formulations manufactured with different methods at different sites (Process D and E) [see "2.A.(1).3) Manufacturing process development (comparability)"]. In this chapter, the NN1841-3788 study is referred to as "Study 3877."

**4.(i).A.(1) Bioequivalence study (5.3.1.2-1, NN1841-3788 [March 2010 to July 2010])**

This study was conducted to assess the bioequivalence and pharmacokinetics of single doses of catridecacog formulations manufactured with Process D or E. A total of 50 healthy men aged 18 to 55 years received a single intravenous injection of catridecacog manufactured with Process D and E at 35 IU/kg (the proposed clinical dose) in a crossover design with a 9-week washout period. Plasma FXIII activity was determined at 3 time points pre-dose and 9 time points between 0.5 hours and 28 days post-dose. Forty-eight subjects completed the study. Of the remaining 2 subjects, one discontinued the study after receiving catridecacog manufactured with Process D and the other discontinued the study after receiving catridecacog manufactured with Process E. In order to eliminate the effect of baseline plasma FXIII activity, pharmacokinetic parameters were calculated after subtracting baseline plasma FXIII activity (the median [0.73-1.60 IU/mL] of 3 baseline measurements) from the post-treatment FXIII activity in each subject.

Bioequivalence was assessed using the area under the plasma activity/concentration-time curve from zero to 28 days ( $AUC_{0-28days}$ ) of both formulations. ( $AUC_{0-28days}$  were estimated based on a linear mixed-effects model using dose-adjusted log-transformed data, by using treatment phase and catridecacog formulation as fixed effects and subjects as random effects.) The ratio of  $AUC_{0-28days}$  of the 2 catridecacog formulations (Process E/Process D) was 1.074 (90% confidence interval [CI], 1.013-1.139); the 90% confidence interval was within the predetermined acceptable range of bioequivalence (0.8-1.25). Table 4-3 lists the pharmacokinetic parameters of both catridecacog formulations calculated based on plasma FXIII activity. All parameters were similar for both formulations.

The applicant explained that the bioequivalence of both formulations has been demonstrated by the above findings.

**Table 4-3. Pharmacokinetic parameters of 2 catridecacog formulations based on plasma FXIII activity (FAS)**

Study drug	AUC <sub>0-28days</sub> (IU·h/mL)	C <sub>30min</sub> (IU/mL)	CL (mL/h/kg)	t <sub>1/2</sub> (h)
Catridecacog (Process D) (N=49)	219.3 ± 50.4	0.85 ± 0.24	0.14 ± 0.05	286.2 ± 199.7
Catridecacog (Process E) (N=49)	234.4 ± 57.0	0.90 ± 0.18* <sup>1</sup>	0.13 ± 0.05	319.8 ± 191.5

Mean ± standard deviation

N = number of subjects, AUC<sub>0-28days</sub> = area under the plasma activity/concentration-time curve from zero to 28 days, C<sub>30min</sub> = plasma FXIII activity at 30 min post-dose, CL = clearance, t<sub>1/2</sub> = elimination half-life

\*<sup>1</sup> Determined after excluding data of 1 subject in whom plasma FXIII activity 30 minutes post-dose was not determined.

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

As for the change of manufacturing process and manufacturing site (from Process D to E), the formulations manufactured with Process D and E were confirmed to have comparable quality attributes [see "2.A.(1).3 Manufacturing process development (comparability)"]. PMDA determined that the results of Study 3788 indicate similar pharmacokinetic profiles of the 2 catridecacog formulations manufactured with Processes D and E, and that the change from Process D to E does not affect the pharmacokinetics of catridecacog.

#### **4.(ii) Summary of clinical pharmacology studies**

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

The applicant submitted evaluation data, i.e., the results of the following clinical pharmacology studies: 2 foreign phase I studies in healthy subjects (5.3.3.1-1, Study F13-1661; and 5.3.3.1-2, Study F13-1662), a Japanese phase I study in healthy subjects (5.3.3.1-3, Study NN1810-3733), a foreign phase I study in patients with congenital FXIII deficiency (5.3.3.2-1: Study F13-1663), a foreign phase III study in patients with congenital FXIII A-subunit deficiency (5.3.5.1-1: Study F13CD-1725) and its extension study (5.3.5.2-1: Study F13CD-3720), and a foreign phase III study in children with congenital FXIII A-subunit deficiency (5.3.3.2-2: Study F13CD-3760). Since Study F13CD-3720 was ongoing at the time of data submission, an interim report including data obtained up to December 31, 2013 was submitted. Unless otherwise specified, values are expressed in mean ± standard deviation. The study identifiers such as Study F13-xxxx, Study NN1810-xxxx, and Study F13CD-xxxx are abbreviated as "Study XXXX."

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

No studies using human biomaterials have been conducted.

##### **4.(ii).A.(2) Studies in healthy subjects**

###### **4.(ii).A.(2).1 Foreign phase I single-dose study (5.3.3.1-1, F13-1661 [January 2003 to May 2003])**

A single intravenous dose of catridecacog (2, 6, 12, 30, or 60 IU/kg) (n = 8/group) or placebo (n = 10) was administered to 50 healthy subjects aged 18 to 65 years, to investigate the safety and

pharmacokinetics of catridecacog after single doses in healthy subjects [for safety, see "4.(iii) Summary of clinical efficacy and safety"]. Plasma FXIII activity was determined at 3 pre-dose time points and 10 time points between 0.5 hour and 28 days post-dose.

The linearity of the pharmacokinetics of catridecacog has been studied using the measured plasma FXIII activity. The difference between the maximum plasma activity ( $C_{max}$ ) and the baseline plasma FXIII activity of individual subjects (the mean of 3 baseline measurements ranging from 0.78 to 2.09 IU/mL) did not increase in proportion to dose when 2 to 12 IU/kg was administered ( $0.26 \pm 0.14$  IU/mL at 2 IU/kg;  $0.52 \pm 0.37$  IU/mL at 6 IU/kg;  $0.57 \pm 0.30$  IU/mL at 12 IU/kg;  $0.76 \pm 0.15$  IU/mL at 30 IU/kg; and  $1.04 \pm 0.14$  IU/mL at 60 IU/kg). The applicant discussed that there were variations in measurements at doses of 2 to 12 IU/kg.

The mean half-life ( $t_{1/2}$ ) of plasma FXIII activity was determined after subtracting baseline FXIII activity (the mean of 3 baseline measurements) from post-dose FXIII activity in each subjects, in order to eliminate the effect of baseline plasma FXIII activity. The mean  $t_{1/2}$  of plasma FXIII activity was 218.8 hours at 30 IU/kg and 272.8 hours at 60 IU/kg. The applicant explained that these findings are largely consistent with the pharmacokinetic parameters in 13 patients with congenital FXIII deficiency receiving a conventional FXIII product ( $t_{1/2}$ , 7.6-10.6 days) (*Thromb Haemost.* 1995;74:622-5).

#### **4.(ii).A.(2).2 Foreign phase I repeated dose study (5.3.3.1-2, F13-1662 [May 2003 to August 2003])**

Catridecacog (12 or 30 IU/kg) or placebo was administered intravenously once daily for 5 days to 24 healthy subjects aged 18 to 65 years ( $n = 8/\text{group}$ ), to investigate the safety and pharmacokinetics of catridecacog after repeated administration [for safety, see "4.(iii) Summary of clinical efficacy and safety"]. Plasma concentrations of FXIII  $A_2B_2$  and free FXIII B-subunits were determined at the following time points: approximately 3 weeks before the start of the treatment; 1 day before the start of the treatment; 1 pre-dose time point on Day 1; 4 time points between 0.5 and 8 hours post-dose on Day 1; 1 pre-dose time point and at 4 hours post-dose from Day 2 to Day 4; 1 pre-dose time point on Day 5; and 9 time points between 0.5 hour post-dose on Day 5 and Day 28. Pharmacokinetic parameters were calculated after subtracting baseline FXIII  $A_2B_2$  concentration (the mean [14.0 to 28.3  $\mu\text{g/mL}$ ] of 3 baseline values measured 3 weeks before the start of treatment, 1 day before the start of treatment, and immediately before administration on Day 1) from post-dose FXIII  $A_2B_2$  concentration in each subject, in order to eliminate the effect of baseline FXIII  $A_2B_2$  concentration (Table 4-5).

The accumulation rate of FXIII  $A_2B_2$  was calculated based on the obtained pharmacokinetic parameters (Day 5 / Day 1) to investigate the accumulation potential of catridecacog. The accumulation rate of FXIII  $A_2B_2$  after repeated administration of catridecacog (Table 4-5) was substantially lower than the accumulation rate estimated from the  $t_{1/2}$  of FXIII  $A_2B_2$  in Study 1661 (15.5). The applicant discussed that this difference was probably due to a decrease in the amount of newly formed FXIII  $A_2B_2$  after

administration with the increasing number of doses, as indicated by the decrease in free FXIII B-subunits with the increasing number of doses (Table 4-5).

**Table 4-5. Pharmacokinetic parameters in healthy subjects receiving repeated administration of catridecacog**

Dose (IU/kg)		FXIII A <sub>2</sub> B <sub>2</sub> concentration		Free FXIII B-subunit concentration	
		AUC <sub>0-24h</sub> (µg·h/mL)	C <sub>max</sub> (µg/mL)	C <sub>pre-dose</sub> (µg/mL)	C <sub>4h</sub> (µg/mL)
12 (N = 8)	Day 1	65.5 ± 28.9	6.13 ± 3.61	2.55 ± 1.53	1.76 ± 1.30
	Day 5	245.0 ± 87.2	14.62 ± 8.34	1.70 ± 0.57	1.26 ± 0.30
	Accumulation rate	4.6 ± 3.6	2.45 ± 1.52	-	-
30 (N = 8)	Day 1	83.1 ± 29.9	6.22 ± 1.70	1.94 ± 1.28	0.83 ± 0.26
	Day 5	342.8 ± 76.1	17.93 ± 3.83	1.40 ± 0.58	1.19 ± 0.33
	Accumulation rate	4.7 ± 2.2	3.16 ± 1.44	-	-

N = number of subjects; AUC<sub>0-24h</sub> = area under the plasma activity/concentration-time curve from zero to 24 hours; C<sub>max</sub> = maximum plasma concentration; C<sub>pre-dose</sub> = plasma concentration before administration; C<sub>4h</sub> = plasma concentration 4 hours post-dose; - = not calculated

#### **4.(ii).A.(2).3 Japanese phase I study (5.3.3.1-3, NN1810-3733 [June 2010 to August 2010])**

A single intravenous dose of catridecacog (12 or 35 IU/kg) or placebo was administered to 24 healthy Japanese subjects aged 20 to 65 years (n = 8/group), to investigate the safety and pharmacokinetics of catridecacog after single doses [for safety, see "4.(iii) Summary of clinical efficacy and safety"]. Plasma FXIII activity was determined at 3 pre-dose time points and 11 time points between 0.5 hour and 28 days post-dose. In order to eliminate the effect of baseline plasma FXIII activity, pharmacokinetic parameters were determined after subtracting baseline plasma FXIIIa activity (the median [0.456-1.25 IU/mL] of 3 baseline measurements) from post-treatment FXIII activity in each subject.

A comparison between the pharmacokinetic parameters in Japanese subjects in Study 3733 and those in non-Japanese subjects in Study 3788 (Table 4-6) revealed differences in clearance (CL), AUC<sub>0-∞</sub>, and t<sub>1/2</sub>.

The applicant discussed the above findings as follows:

Catridecacog is planned to be administered every 28 days in the clinical setting. The plasma FXIII activity on Day 28 was similar for Studies 3733 and 3788 (Table 4-6). This result suggests that catridecacog 35 IU/kg (the proposed clinical dose) is able to ensure a plasma FXIII activity of 0.1 IU/mL, which is required to obtain sufficient preventive effect against bleeding events, in Japanese patients as well [see "4.(iii).B.(6).1 Basis for selecting the dosage regimen of routine prophylactic treatment of bleeding"], and the differences in CL, AUC<sub>0-∞</sub>, and t<sub>1/2</sub> were not considered clinically relevant.

**Table 4-6. Pharmacokinetic parameters based on plasma FXIII activity in Japanese and non-Japanese healthy subjects**

Study Identifier	Dose (IU/kg)	AUC <sub>0-∞</sub> (IU·h/mL)	C <sub>30min</sub> (IU/mL)	C <sub>trough,28day</sub> (IU/mL)	CL (mL/h/kg)	t <sub>1/2</sub> (h)
NN1841-3788 (N = 50* <sup>1</sup> )	35	301 ± 142	0.87 ± 0.21* <sup>2</sup>	0.10 ± 0.09	0.14 ± 0.05	303 ± 195
NN1810-3733 (N = 8)	35	185 ± 56	0.77 ± 0.10	0.10 ± 0.06	0.21 ± 0.08	187 ± 69

N = number of subjects; AUC<sub>0-∞</sub> = area under the plasma activity/concentration-time curve from zero to infinity; C<sub>30min</sub> = plasma FXIII activity at 30 min post-dose; C<sub>trough,28day</sub> = Plasma FXIII activity on Day 28; CL = clearance; t<sub>1/2</sub> = elimination half-life

\*<sup>1</sup> A total of 98 doses of catridecacog formulations were administered (49 doses, Processes D; 49 doses, Processes E)

\*<sup>2</sup>: Obtained from data of 49 subjects, after excluding 1 subject with missing data on plasma FXIII activity 30 min post-dose.

#### **4.(ii).A.(3) Studies in patients**

##### **4.(ii).A.(3).1 Foreign phase I clinical study (5.3.3.2-1, F13-1663 [March 2003 to October 2003])**

A single intravenous dose of catridecacog (2, 7, 24, 60, or 89 IU/kg) was administered to 9 patients with congenital FXIII deficiency who were aged ≥18 years (3 patients in the 60 IU/kg group and 2 patients each in other dose groups; 2 of the 9 patients received catridecacog at 2 different doses). The study investigated the safety and pharmacokinetics of catridecacog in patients with congenital FXIII deficiency [for safety, see "4.(iii) Summary of clinical efficacy and safety"]. Plasma FXIII activity was determined at 2 pre-dose time points and 10 time points between 0.5 hour and 28 days post-dose. Pharmacokinetic profile was assessed for patients in the 24, 60, and 89 IU/kg groups. Plasma FXIII activity at 0.5 hours post-dose increased proportionally to the dose (0.64 IU/mL at 24 IU/kg; 1.37 -1.52 IU/mL at 60 IU/kg; 1.95-2.27 IU/mL at 89 IU/kg). In all patients (other than 1 patient in the 60 IU/kg group, who was found to have FXIII B-subunit deficiency), AUC<sub>0-∞</sub> increased proportionally to the dose. In the patient with FXIII B-subunit deficiency, t<sub>1/2</sub> was 9 hours, AUC<sub>0-∞</sub> was 13.6 IU·h/mL, and CL was 4.28 mL/h/kg. The patient with FXIII B-subunit deficiency had a shorter t<sub>1/2</sub>, smaller AUC<sub>0-∞</sub>, and higher CL than other patients receiving 60 IU/kg (t<sub>1/2</sub>, 149-156 hours; AUC<sub>0-∞</sub>, 239-304 IU·h/mL; CL, 0.20-0.25 mL/h/kg).

The applicant explained as follows:

Pharmacokinetic data obtained from this study and Studies 1661 and 1662 in healthy subjects suggest that the mean trough plasma FXIII activity at steady state is expected to be approximately 0.1 IU/mL in patients receiving catridecacog 35 IU/kg every 28 days. Therefore 35 IU/kg dose every 4 weeks was selected for the phase III studies in patients with congenital FXIII A-subunit deficiency.

##### **4.(ii).A.(3).2 Foreign phase III study (5.3.5.1-1, F13CD-1725 [August 2008 to April 2010])**

Catridecacog 35 IU/kg was intravenously administered every 4 weeks (28 ± 2 days) for 52 weeks (13 injections in total) to 41 patients with congenital FXIII A-subunit deficiency aged ≥6 years, to investigate the efficacy and safety of routine prophylactic treatment with catridecacog in patients with congenital FXIII A-subunit deficiency [for efficacy and safety, see "4.(iii) Summary of clinical efficacy and safety"]. Table 4-7 summarizes the pharmacokinetic parameters of catridecacog in Study 1725.



**4.(ii).A.(3).3 Multi-regional phase III extension study (5.3.5.2-1, F13CD-3720 [ongoing since September 2009 (data cut-off of December 31, 2013)])**

Catridecacog 35 IU/kg was intravenously administered every 4 weeks ( $28 \pm 2$  days) for  $\geq 52$  weeks to patients with congenital FXIII A-subunit deficiency aged  $\geq 6$  years (34 patients who continued treatment from Study 1725, and 26 patients, including 5 Japanese patients, who started catridecacog therapy in this study), to investigate the long-term safety of routine prophylactic treatment with catridecacog in patients with congenital FXIII A-subunit deficiency [for long-term safety, see "4.(iii) Summary of clinical efficacy and safety"].

In total, 23 patients (14 patients continuing treatment from Study 1725 and 9 non-Japanese patients starting treatment in this study) consented to additional blood sampling for the determination of pharmacokinetic parameters. They received at least 10 doses of catridecacog and were considered to have reached a steady state. In the 23 patients, plasma FXIII activity was determined at a pre-dose time point and at 7 time points between 1 hour and 28 days post-dose. The applicant explained that pharmacokinetic parameters at steady state in Study 3720 were largely consistent with those in Study 1725 (Table 4-7).

**Table 4-7. Pharmacokinetic parameters based on plasma FXIII activity at steady state**

Study Identifier	AUC <sub>0-28days</sub> (IU·h/mL)	C <sub>max</sub> (IU/mL)	C <sub>trough</sub> (IU/mL)	t <sub>1/2</sub> (h)
F13CD-1725 (N = 41)	248.2 ± 56.7	0.77 ± 0.20	0.19 ± 0.05	289 ± 60
F13CD-3720 (N = 23)	240.4 ± 49.0* <sup>1</sup>	0.89 ± 0.20	0.17 ± 0.06* <sup>2</sup>	338 ± 83* <sup>3</sup>

N = number of patients; AUC<sub>0-28days</sub> = area under the plasma activity/concentration-time curve from zero to 28 days; C<sub>max</sub> = maximum plasma FXIII activity; C<sub>trough</sub> = trough plasma FXIII activity; t<sub>1/2</sub> = elimination half-life

\*<sup>1</sup> Calculated using data of 19 patients, after excluding 4 patients with missing data at  $\geq 2$  time points between Day 14 and Day 28.

\*<sup>2</sup> Calculated using data of 21 patients, after excluding 2 patients with missing data on Day 28.

\*<sup>3</sup> Calculated using data of 20 patients, after excluding 3 patients with missing data at  $\geq 2$  time points between Day 3 and Day 28.

In 27 of 60 patients receiving catridecacog, trough plasma FXIII activity was  $< 0.10$  IU/mL at some time points, but the  $< 0.10$  IU/mL values were unrelated to bleeding episodes requiring treatment with FXIII-containing products, including cryoprecipitate, fresh frozen plasma, and plasma-derived FXIII products.

The applicant explained that the results of Studies 1725 and 3720 indicate that catridecacog 35 IU/kg every 4 weeks is able to maintain a plasma FXIII activity of 0.1 IU/mL, which is required to prevent bleeding episodes in patients with congenital FXIII A-subunit deficiency [see "4.(iii).B.(6).1) Basis for selecting the dosage regimen of routine prophylactic treatment of bleeding"].

#### 4.(ii).A.(3).4 Foreign phase III study (5.3.3.2-2, F13CD-3760 [November 2010 to January 2012])

A single intravenous dose of catridecacog 35 IU/kg was administered to 6 children aged 1 to <6 years with congenital FXIII A-subunit deficiency, to investigate the pharmacokinetics and safety of single-dose catridecacog in children with congenital FXIII A-subunit deficiency [for safety, see "4.(iii) Summary of clinical efficacy and safety"]. Plasma FXIII activity was determined at a pre-dose time point and 6 time points between 0.5 hours and 30 days post-dose. The median  $t_{1/2}$  was approximately 15 days (range, 10-25 days). The applicant explained that although the pharmacokinetic profile of catridecacog differed by age in cynomolgus monkeys [see "Single-dose studies" in "3.(ii).A.(1) Absorption"], the pharmacokinetic parameters obtained in Study 3760 (Table 4-8) were similar to those obtained in Studies 1725 and 3720 involving patients aged  $\geq 6$  years.

**Table 4-8. Pharmacokinetic parameters based on plasma FXIII activity in children aged 1 to <6 years with congenital FXIII A-subunit deficiency (FAS)**

N	AUC <sub>0-30days</sub> (IU·h/mL)	C <sub>max</sub> (IU/mL)	CL (mL/h/kg)	t <sub>1/2</sub> (h)
6	250 ± 31	0.69 ± 0.14	0.15 ± 0.02	378 ± 129

N = number of patients; AUC<sub>0-30days</sub> = area under the plasma activity/concentration-time curve from zero to 30 days; C<sub>max</sub> = maximum plasma FXIII activity; CL = clearance; t<sub>1/2</sub> = elimination half-life

#### 4.(ii).A.(4) Studies on drug interactions

No studies on drug interactions were conducted.

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

PMDA concluded as follows:

The submitted data indicate that pharmacokinetic parameters of catridecacog in patients with congenital FXIII A-subunit deficiency are consistent across the clinical studies of catridecacog with no clinically relevant effects of age or ethnicity. Trough plasma FXIII activity following administration of catridecacog 35 IU/kg every 4 weeks was shown to be approximately 0.1 IU/mL.

#### 4.(iii) Summary of clinical efficacy and safety

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

The applicant submitted evaluation data on the efficacy and safety (the results of 4 foreign phase I studies, a phase I Japanese study, and 2 foreign phase III studies, and interim analysis results of a multi-regional phase III study) and reference data (the interim analysis results of a foreign phase III study). Table 4-9 lists the clinical studies of catridecacog.

**Table 4-9. Clinical studies on the efficacy and safety of catridecacog**

	Study identifier	Phase	Countries (No. of institutions)	Subjects	No. of subjects exposed	Outline of dosage regimens
<b>Evaluation data</b>						
Foreign	F13-1661	I	UK (1)	Healthy subjects (aged 18 to ≤65 years)	n = 50 (catridecacog, 40; placebo, 10)	Single dose of catridecacog 2, 6, 12, 30, or 60 IU/kg or placebo
Foreign	F13-1662	I	UK (1)	Healthy subjects (aged 18 to ≤65 years)	n = 24 (catridecacog, 16; placebo, 8)	Catridecacog 12 or 30 IU/kg or placebo once daily for 5 days
Foreign	NN1841-3788	I	UK (1)	Healthy men (aged 18 to ≤55 years)	n = 50	Single dose of catridecacog 35 IU/kg (Processes D and E formulations with a 9-week washout period)
Japan	NN1810-3733	I	Japan (1)	Healthy men (aged 20 to ≤ 65 years)	n = 24 (catridecacog, 16; placebo, 8)	Single dose of catridecacog 12 or 35 IU/kg or placebo
Foreign	F13-1663	I	US (1)	Patients with congenital FXIII deficiency (aged ≥18 years)	n = 9 (2 patients received 2 different doses) (2 patients each in the 2, 7, 24, and 89 IU/kg groups; 3 patients in the 60 IU/kg group)	Single dose of catridecacog 2, 7, 24, 60, or 89 IU/kg
Foreign	F13CD-1725	III	Austria (1), Canada (1), Finland (1), France (1), Germany (3), Israel (2), Italy (1), Spain (1), Switzerland (1), UK (3), US (8)	Patients with congenital FXIII A-subunit deficiency (aged ≥6 years)	n = 41	Catridecacog 35 IU/kg every 4 weeks
Multi-regional	F13CD-3720	III	Austria (1), Canada (1), Finland (1), France (4), Germany (4), Israel (1), Italy (1), Japan (2), Spain (2), Switzerland (1), UK (4), US (12)	Patients with congenital FXIII A-subunit deficiency (aged ≥6 years)	n = 60 (data cut-off, December 31, 2013)	Routine replacement therapy: catridecacog 35 IU/kg every 4 weeks  On-demand treatment for breakthrough bleedings: single dose of catridecacog 35 IU/kg
Foreign	F13CD-3760	III	UK (2), Israel (1), US (2)	Patients with congenital FXIII A-subunit deficiency (aged 1 to < 6 years)	n = 6	Single dose of catridecacog 35 IU/kg
<b>Reference data</b>						
Foreign	F13CD-3835	III	UK (2), Israel (1), US (2)	Patients with congenital FXIII A-subunit deficiency who completed Study F13CD-3760 (aged 1 to ≤ 6 years)	n = 6 (data cut-off, January 15, 2013)	Catridecacog 35 IU/kg every 4 weeks

**4.(iii).A.(1) Foreign phase I study (5.3.3.1-1: F13-1661 [January 2003 to May 2003])**

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in healthy subjects aged 18 to ≤65 years with a target sample size of 50 (n = 10 for each dose [catridecacog, n = 8; placebo, n = 2]) to assess the safety and pharmacokinetics following a single dose of catridecacog.

A single dose of catridecacog 2, 6, 12, 30, or 60 IU/kg or placebo was administered as a slow intravenous injection for 3 to 5 minutes.

In this study, 50 subjects received a study drug, and all subjects were assessed for safety and pharmacokinetics. The results of pharmacokinetic assessment are described in "4.(ii) Summary of clinical pharmacology studies."

Safety analysis revealed that 80.0% of the subjects receiving catridecacog (32 of 40 subjects) experienced a total of 89 adverse events during the study: 20 events in 7 of 8 subjects (87.5%) in the 2 IU/kg group; 9 events in 5 of 8 subjects (62.5%) in the 6 IU/kg group; 25 events in 7 of 8 subjects (87.5%) in the 12 IU/kg group; 16 events in 6 of 8 subjects (75.0%) in the 30 IU/kg group; and 19 events in 7 of 8 subjects (87.5%) in the 60 IU/kg group. In the placebo group, 26 adverse events developed in 6 of 10 subjects (60.0%). Table 4-10 lists the adverse events that developed in ≥2 subjects receiving catridecacog.

**Table 4-10. Adverse events developing in ≥2 subjects receiving catridecacog (safety analysis set)**

	Placebo (N = 10)		Catridecacog									
			2 IU/kg (N = 8)		6 IU/kg (N = 8)		12 IU/kg (N = 8)		30 IU/kg (N = 8)		60 IU/kg (N = 8)	
	No. of subjects (%)	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	No. of events
Headache	4 (40)	8	4 (50)	7	3 (37.5)	4	4 (50)	10	3 (37.5)	4	3 (37.5)	8
Fibrin D dimer increased	2 (20)	4	2 (25)	2	0 (0)	0	0 (0)	0	2 (25)	2	0 (0)	0
Cramp	1 (10)	2	0 (0)	6	0 (0)	0	2 (25)	2	1 (12.5)	1	1 (12.5)	1
Pain in extremity	1 (10)	1	1 (12.5)	1	0 (0)	0	2 (25)	2	0 (0)	0	1 (12.5)	1
Nasopharyngitis	0 (0)	0	2 (25)	2	0 (0)	0	1 (12.5)	1	0 (0)	0	0 (0)	0
Thrombin time prolonged	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	3 (37.5)	3
Upper respiratory tract infection	1 (10)	1	1 (12.5)	1	0 (0)	0	1 (12.5)	1	1 (12.5)	1	0 (0)	0
Abdominal pain upper	0 (0)	0	1 (12.5)	1	0 (0)	0	1 (12.5)	1	0 (0)	0	0 (0)	0
Excoriation	0 (0)	0	1 (12.5)	1	1 (12.5)	1	0 (0)	0	0 (0)	0	0 (0)	0
Contusion	0 (0)	0	1 (12.5)	1	0 (0)	0	0 (0)	0	1 (12.5)	1	0 (0)	0
Cough	0 (0)	0	0 (0)	0	1 (12.5)	1	0 (0)	0	1 (12.5)	1	0 (0)	0

N = number of subjects

Six subjects experienced 6 adverse events related or possibly related to the study drug (adverse drug reactions): 1 event (headache) in 1 subject in the 2 IU/kg group; 2 events in 2 subjects in the 6 IU/kg group (headache in one subject, aspartate aminotransferase increased in the other); 1 event (nausea) in 1 subject in the 12 IU/kg group; and 2 events (thrombin time prolonged) in 2 subjects in the 60 IU/kg

group. In the placebo group, 1 event (headache) occurred in 1 subject. The outcome was “resolved” in all adverse drug reactions.

None of the subjects experienced serious adverse events including death or adverse events resulting in discontinuation of treatment.

**4.(iii).A.(2) Foreign phase I study (5.3.3.1-2: F13-1662 [May 2003 to August 2003])**

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in healthy subjects aged 18 to ≤65 years with a target sample size of 24 (n = 12 for each dose [catridecacog, n = 8; placebo, n = 4]) to assess the safety and pharmacokinetics following repeated doses of catridecacog.

Subjects received intravenous injections of catridecacog 12 or 30 IU/kg or placebo at a rate of ≤2 mL/min once daily for 5 days.

In this study, 24 subjects received catridecacog and all of them were assessed for safety and pharmacokinetics. The results of pharmacokinetic assessment are described in "4.(ii) Summary of clinical pharmacology studies."

During the study period, 44 adverse events developed in 12 of 16 subjects (75.0%) receiving catridecacog: 24 events in 6 of 8 subjects (75.0%) in the 12 IU/kg group and 20 events in 6 of 8 subjects (75.0%) in the 30 IU/kg group. In the placebo group, 30 events developed in 6 of 8 subjects (75.0%). Table 4-11 lists the adverse events that developed in ≥2 subjects receiving catridecacog.

**Table 4-11. Adverse events developing in ≥2 subjects receiving catridecacog (safety analysis set)**

	Placebo (N = 8)		Catridecacog			
			12 IU/kg (N = 8)		30 IU/kg (N = 8)	
	No. of subjects (%)	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)	No. of events
Headache	5 (62.5)	13	4 (50.0)	8	4 (50.0)	7
Somnolence	1 (12.5)	1	2 (25.0)	2	1 (12.5)	2
Paraesthesia	0 (0.0)	0	1 (12.5)	1	1 (12.5)	1
Upper respiratory tract infection NOS	1 (12.5)	1	3 (37.5)	3	0 (0.0)	0
Fatigue	2 (25.0)	3	2 (25.0)	2	0 (0.0)	0
Dysmenorrhoea	0 (0.0)	0	1 (12.5)	1	1 (12.5)	1

N = number of subjects

No adverse drug reactions were reported.

None of the subjects experienced serious adverse events including death or adverse events resulting in discontinuation of treatment.

#### 4.(iii).A.(3) Foreign phase I study (5.3.1.2-1, NN1841-3788 [March 2010 to July 2010])

A randomized, double-blind, 2-group, 2-phase cross-over study was conducted in healthy subjects aged 18 to  $\leq 55$  years with a target sample size of 50 to assess the bioequivalence and pharmacokinetics following single doses of 2 different catridecacog formulations manufactured with Process D and E.

Subjects received single intravenous injections of catridecacog 35 IU/kg manufactured with Process D and E at a rate of  $\leq 2$  mL/min. A 9-week washout period was scheduled between the 2 doses.

Fifty subjects received the catridecacog formulations and 48 subjects completed the study, except 2 subjects who discontinued the study after administration of catridecacog manufactured with Process D and E (1 subject each). All patients who received the study drug were included in the full analysis set (FAS) and safety analysis set. Pharmacokinetic analysis was conducted for the FAS population. The results of pharmacokinetic assessment are described in "4.(ii) Summary of clinical pharmacology studies."

During the study period, 21 adverse events developed in 15 of 49 subjects (30.6%) receiving catridecacog manufactured with Process D, and 25 adverse events in 17 of 49 subjects (34.7%) receiving catridecacog manufactured with Process E. Table 4-12 lists the adverse events that developed in  $\geq 2$  subjects.

**Table 4-12. Adverse events developing in  $\geq 2$  subjects (Safety analysis set)**

	Catridecacog manufactured with Process D (N =49)		Catridecacog manufactured with Process E (N =49)	
	No. of subjects (%)	No. of events	No. of subjects (%)	No. of events
Headache	1 (2.0)	3	5 (10.2)	7
Nasopharyngitis	3(6.1)	3	3 (6.1)	3
Toothache	2(4.1)	2	1 (2.0)	1
Pain in extremity	0 (0.0)	0	2 (4.1)	2
Influenza	1 (2.0)	1	1 (2.0)	1
Arthropod bite	0 (0.0)	0	2 (4.1)	2

N = number of subjects

Following the administration of the Process D formulation, 2 subjects experienced 2 adverse drug reactions (anti-catridecacog non-neutralizing antibody test positive [1 subject] and muscle tightness [1 subject]). Following the administration of the Process E formulation, 2 subjects experienced 3 adverse drug reactions (pain in extremity and headache [1 subject], and myalgia [1 subject]). All events resolved other than anti-catridecacog non-neutralizing antibody test positive. The subject with anti-catridecacog non-neutralizing antibody test positive discontinued the study after the administration of the Process D formulation because of positive results for antibodies. As of the data lock date, the outcome of this event was considered "not resolved" because of the lack of follow-up test results at 6 months after discontinuation. The follow-up test conducted 6 months after discontinuation (after the data lock date) revealed negative results for antibodies; the outcome of the event was therefore reported as "resolved."

None of the subjects experienced serious adverse events including death.

**4.(iii).A.(4) Phase I Japanese study (5.3.3.1-3, NN1810-3733 [June 2010 to August 2010])**

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in healthy men aged 20 to  $\leq 65$  years with a target sample size of 24 (n = 12 for each dose [catridecacog, n = 8; placebo, n = 4]) to assess the safety and pharmacokinetics of single doses of catridecacog.

Subjects received a single intravenous administration of catridecacog 12 or 35 IU/kg or placebo at a rate of  $\leq 2$  mL/min.

In this study, 24 subjects received a study drug, and all subjects were included in the safety analysis set and FAS. Pharmacokinetic analysis was conducted for the FAS population. The results of pharmacokinetic assessment are described in "4.(ii) Summary of clinical pharmacology studies."

During the study period, 1 of 8 subjects (12.5%) in the placebo group experienced an adverse event of aspartate aminotransferase increased, but a causal relationship with the study drug was ruled out. No adverse events were reported in the catridecacog group.

None of the subjects experienced serious adverse events including death or adverse events resulting in discontinuation of treatment.

**4.(iii).A.(5) Foreign phase I study (5.3.3.2-1, F13-1663 [March 2003 to October 2003])**

An open-label non-controlled study was conducted in patients with congenital FXIII deficiency aged  $\geq 18$  years with a target sample size of 10 to 12 (n = 2 for each dose; each patient may receive up to 2 different doses of catridecacog) to assess the safety and pharmacokinetics of catridecacog. Patients with congenital FXIII B-subunit deficiency may be enrolled in the study, but patient enrollment was to be continued until 2 patients with congenital FXIII A-subunit deficiency are assigned to each dose group.

Patients received a slow single intravenous administration of catridecacog 2, 7, 24, 60, or 89 IU/kg for 3 to 5 minutes.

In this study, 9 patients received catridecacog: 2 patients each received 2, 7, 24, or 89 IU/kg, and 3 patients, including 1 patient with congenital FXIII B-subunit deficiency, received 60 IU/kg (2 of the 9 patients received 2 single doses at 2 and 89 IU/kg). All patients receiving catridecacog were included in safety analysis. Pharmacokinetic analysis was conducted in 7 patients receiving 24, 60, or 89 IU/kg. Four patients receiving 2 or 7 IU/kg were excluded from the pharmacokinetic analysis, because they received prophylactic treatment with a FXIII-containing product 72 hours after the administration of catridecacog. The results of pharmacokinetic assessment are described in "4.(ii) Summary of clinical pharmacology studies."

In total, 11 adverse events occurred in 4 of the 11 cases (36.4%) during the study period: 6 events in 1 patient in the 7 IU/kg group, 1 event in 1 patient in the 24 IU/kg group, and 4 events in 2 patients in the 60 IU/kg group. Table 4-13 lists adverse events reported in the study.

**Table 4-13. Adverse events (safety analysis set)**

	2 IU/kg (N = 2)		7 IU/kg (N = 2)		24 IU/kg (N = 2)		60 IU/kg (N = 3)		89 IU/kg (N = 2)	
	No. of patients	No. of events	No. of patients	No. of events	No. of patients	No. of events	No. of patients	No. of events	No. of patients	No. of events
Headache	0	0	1	1	1	1	1	1	0	0
Arthralgia	0	0	1	2	0	0	1	1	0	0
Contusion	0	0	1	1	0	0	0	0	0	0
Pain NOS	0	0	0	0	0	0	1	1	0	0
Pain in extremity	0	0	0	0	0	0	1	1	0	0
Pharyngolaryngeal pain	0	0	1	1	0	0	0	0	0	0
Throat tightness	0	0	1	1	0	0	0	0	0	0

N = number of patients

No adverse drug reactions were reported.

None of the patients experienced serious adverse events including death or adverse events resulting in discontinuation of treatment.

#### **4.(iii).A.(6) Foreign phase III study (5.3.5.1-1, F13CD-1725 [August 2008 to April 2010])**

An open-label non-controlled study was conducted in patients with congenital FXIII A-subunit deficiency aged  $\geq 6$  years with a target sample size of 40 to assess the efficacy and safety of routine prophylactic treatment with catridecacog.

Catridecacog 35 IU/kg was administered intravenously at a rate of  $\leq 2$  mL/min every 4 weeks ( $28 \pm 2$  days) for 52 weeks (13 injections, in total).

In total, 41 patients received catridecacog. All patients were included in the FAS and safety analysis set. The efficacy was assessed for the FAS population.

The number of exposures to catridecacog per patient (mean  $\pm$  standard deviation) was  $11.5 \pm 3.6$  (range, 2-14).

The primary endpoint was the rate of bleeding episodes requiring treatment with a FXIII-containing product (number per patient year) during the treatment period. During the observation period (mean, 322 days), 4 patients experienced 5 bleeding episodes requiring a treatment with a FXIII containing product, with the mean yearly bleeding rate of 0.138 per patient year. The yearly bleeding rate was



estimated based on a Poisson regression model, with adjustment for the mean age (26.4 years) of the study population. (The estimate is from a Poisson model with age as a covariate and the total observation time during the treatment period as an offset in the model. The estimated rate is adjusted for overdispersion.) The estimated rate was 0.048 per patient year (95% CI, 0.0094-0.2501). The upper limit of the 95% confidence interval was thus below the predefined threshold of <2.91, the yearly bleeding rate in patients without routine prophylactic treatment (calculated from the data of Study F13CD-QUEST, [see "4.(iii).B.(2).1).(a) Evaluation methods"]). The yearly bleeding rate in patients receiving routine prophylactic treatment with catridecacog was statistically significantly lower than the predefined threshold. The protocol of Study 1725 did not specify that yearly bleeding rate should be adjusted for the mean age of the study population in the Poisson regression model analysis. However, even when adjusted for 31.7 years (the mean age of the 16 patients without routine prophylactic treatment in Study F13CD-QUEST), the yearly bleeding rate is estimated to be 0.025 per patient year. This suggests that the yearly bleeding rate in Study 1725 is low regardless of the age used for adjustment.

During the study period, 231 adverse events developed in 32 of 41 patients (78.0%). Table 4-14 lists adverse events that developed in >5.0% of the study population.

**Table 4-14. Adverse events developing in >5.0% of the study population (Safety analysis set, N=41)**

Adverse events	No. of patients (%)	No. of events	Adverse events	No. of patients (%)	No. of events
Diarrhoea	3 (7.3)	3	Incorrect dose administered	4 (9.8)	11
Toothache	3 (7.3)	5	Antibody test positive	4 (9.8)	4
Vomiting	3 (7.3)	3	Arthralgia	5 (12.2)	5
Pyrexia	7 (17.1)	7	Pain in extremity	4 (9.8)	4
Influenza	4 (9.8)	4	Headache	12 (29.3)	21
Nasopharyngitis	8 (19.5)	11	Cough	3 (7.3)	4
Urinary tract infection	3 (7.3)	3	Nasal congestion	5 (12.2)	6
Excoriation	3 (7.3)	3	Oropharyngeal pain	4 (9.8)	6

N = number of patients

Nine patients (22.0%) experienced 13 adverse drug reactions: 4 events of anti-catridecacog non-neutralizing antibody test positive; 3 events of incorrect dose administered; and 1 event each of injection site pain, fibrin D dimer increased, pain in extremity, headache, leukopenia, and neutropenia. The outcome of pain in extremity was “not resolved” at approximately 2 months after onset, while the outcome of other adverse drug reactions was “resolved.” The outcome of pain in extremity was reported as “resolved” at 10 months after onset during Study 3720, the extension study to Study 1725.

No deaths were reported. Six patients (14.6%) experienced 8 serious adverse events: 3 events of anti-catridecacog non-neutralizing antibody test positive; and 1 event each of diverticulitis, non-cardiac chest pain, headache, road traffic accident, and small intestinal obstruction. For all serious adverse events (other than the 3 events of anti-catridecacog non-neutralizing antibody test positive), a causal

relationship with catridecacog therapy was ruled out, and the outcome was reported as “resolved.” Four patients (9.8%) experienced 5 adverse events resulting in discontinuation of treatment: 3 events of anti-catridecacog non-neutralizing antibody test positive; and 1 event each of leukopenia and neutropenia.

**4.(iii).A.(7) Multi-regional phase III extension study (5.3.5.2-1, F13CD-3720 [ongoing since September 2009 (data cut-off of December 31, 2013)])**

An open-label uncontrolled study was conducted in patients who completed Study 1725 with a target sample size of 25 to 40 patients to evaluate the long-term safety of routine prophylactic treatment with catridecacog. During the study period, the study protocol was amended to include patients with congenital FXIII A-subunit deficiency aged  $\geq 6$  years who discontinued or did not participate in Study 1725, and to increase the target sample size to 33 to 60 patients.

Catridecacog 35 IU/kg was administered intravenously at a rate of  $\leq 2$  mL/min every 4 weeks ( $28 \pm 2$  days) for  $\geq 52$  weeks. The original protocol stated that a conventional FXIII-containing product should be used in case of a bleeding episode requiring treatment with a FXIII-containing product. During the course of the study, however, the protocol was amended to require that additional 35 IU/kg catridecacog be used, wherever possible, for the treatment of such bleeding episodes. The amendment was made at the request of the European Medicines Agency.

Up to the cut-off date of December 31, 2013, 60 patients received catridecacog and were included in the safety analysis set and FAS. The efficacy analysis was conducted for the FAS population. Five Japanese patients were enrolled in this study.

The number of exposures to catridecacog per patient (mean  $\pm$  standard deviation) was  $34.2 \pm 15.2$  (range, 2-54).

Up to the cut-off date (December 31, 2013), 55 of 60 patients (91.7%) experienced a total of 796 adverse events. Table 4-15 lists adverse events that developed in  $\geq 5.0\%$  of patients.

**Table 4-15. Adverse events developing in  $\geq 5.0\%$  of patients (Safety analysis set, N = 60)**

Adverse events	No. of patients (%)	No. of events	Adverse events	No. of patients (%)	No. of events
Anaemia	4 (6.7)	6	Injury	4 (6.7)	4
Ear pain	4 (6.7)	4	Joint injury	4 (6.7)	6
Abdominal pain	5 (8.3)	6	Laceration	6 (10.0)	7
Constipation	5 (8.3)	5	Ligament sprain	7 (11.7)	10
Dental caries	3 (5.0)	4	Limb injury	5 (8.3)	10
Diarrhoea	3 (5.0)	3	Post-traumatic pain	3 (5.0)	4
Dyspepsia	5 (8.3)	12	Procedural pain	3 (5.0)	3
Nausea	6 (10.0)	6	Road traffic accident	4 (6.7)	4
Toothache	4 (6.7)	6	Thermal burn	6 (10.0)	6
Vomiting	3 (5.0)	4	Wound	3 (5.0)	3
Fatigue	3 (5.0)	3	White blood cells urine positive	3 (5.0)	3
Pyrexia	5 (8.3)	10	Arthralgia	9 (15.0)	23
Seasonal allergy	3 (5.0)	4	Back pain	10 (16.7)	13
Bronchitis	3 (5.0)	5	Musculoskeletal pain	5 (8.3)	6
Folliculitis	3 (5.0)	5	Musculoskeletal stiffness	3 (5.0)	3
Gastroenteritis	8 (13.3)	9	Myalgia	3 (5.0)	5
Influenza	6 (10.0)	6	Neck pain	4 (6.7)	4
Nasopharyngitis	17 (28.3)	38	Pain in extremity	11 (18.3)	24
Sinusitis	12 (20.0)	18	Headache	18 (30.0)	75
Upper respiratory tract infection	14 (23.3)	21	Haematuria	3 (5.0)	3
Viral infection	3 (5.0)	3	Cough	12 (20.0)	28
Arthropod bite	3 (5.0)	3	Nasal congestion	7 (11.7)	18
Contusion	9 (15.0)	15	Oropharyngeal pain	11 (18.3)	30
Excoriation	5 (8.3)	6	Rhinorrhoea	3 (5.0)	4
Fall	8 (13.3)	12	Acne	3 (5.0)	4
Head injury	4 (6.7)	7	Pruritus	3 (5.0)	5
Incorrect dose administered	5 (8.3)	7	Rash	5 (8.3)	8

N = number of patients

Six patients (10.0%) experienced 7 adverse drug reactions: 1 event each of leukopenia, rectal haemorrhage, incorrect dose administered, limb injury, overdose, blood alkaline phosphatase increased, and arthralgia. The outcome of all adverse drug reactions was “resolved”.

No deaths were reported up to the cut-off date. Ten patients (16.7%) experienced 16 serious adverse events: 2 events each of fall, road traffic accident, and head injury; 1 event each of chest injury, inguinal hernia, diverticulitis, laceration, otitis media chronic, cerebral ischaemia, headache, suicide attempt, multiple fractures, and spinal cord injury. A causal relationship with catridecacog was ruled out for all serious adverse events. The outcome was “not resolved” for spinal cord injury due to road traffic accident and “resolved with sequelae” for fall. The outcome of other serious adverse events was “resolved.” There were no adverse events resulting in discontinuation of treatment.

All of the 5 Japanese patients (100%) experienced 29 adverse events (Table 4-16) (all included in the safety analysis set). One patient experienced 1 adverse drug reaction (blood alkaline phosphatase increased). None of the patients experienced serious adverse events including death.

**Table 4-16. Adverse events observed in 5 Japanese patients**

Adverse events	No. of patients (%)	No. of events
Vertigo	1 (20.0)	1
Chest pain	1 (20.0)	2
Influenza	1 (20.0)	1
Nasopharyngitis	4 (80.0)	9
Contusion	1 (20.0)	1
Activated partial thromboplastin time shortened	1 (20.0)	1
Blood alkaline phosphatase increased	1 (20.0)	1
Glucose urine present	1 (20.0)	1
White blood cells urine positive	3 (60.0)	3
Intervertebral disc protrusion	1 (20.0)	1
Musculoskeletal stiffness	1 (20.0)	1
Neck pain	1 (20.0)	1
Pain in extremity	1 (20.0)	1
Headache	1 (20.0)	2
Asthma	1 (20.0)	1
Cough	1 (20.0)	1
Dermatitis contact	1 (20.0)	1
Total	5 (100)	29

The secondary endpoint was the efficacy of routine prophylactic treatment with catridecacog for bleeding. This endpoint was evaluated with the rate (number per patient year) of bleeding episodes requiring treatment with a FXIII-containing product during the treatment period. During the mean follow-up period of 973 days, 6 patients experienced a total of 7 bleeding episodes requiring treatment with a FXIII-containing product, and the mean yearly bleeding rate was 0.042 per patient year. Based on a Poisson regression model. (The estimate is from a Poisson model with age as a covariate and the total observation time during the treatment period as an offset in the model, and the estimated rate is adjusted for overdispersion.) The estimate of yearly bleeding rate, adjusted for the mean age of the study population of 31.0 years, was 0.015 per patient year (95% CI, 0.003-0.072).

The efficacy of on-demand treatment of bleeding, the additional secondary endpoint, was assessed by the patients themselves in cooperation with physicians at approximately 8 hours post-dose according to the 4-rank scale shown in Table 4-17. By the cut-off date, 6 patients experienced 7 bleeding episodes requiring treatment with a FXIII-containing product. Among the episodes, 1 bleeding episode in 1 patient was treated with catridecacog, and the efficacy was rated "excellent."

None of the Japanese patients experienced bleeding episodes requiring treatment with a FXIII-containing product by the cut-off date.

**Table 4-17. Four-rank scale**

Excellent	Abrupt pain relief and/or bleeding stopped or substantially reduced within 8 hours after administration of rFXIII
Good/Effective	Some pain relief and/or improvement in signs of bleeding within approximately 8 hours after infusion of product, but not requiring more than 1 infusion for complete bleeding arrest.
Moderate/Partly effective	Slight beneficial effect on pain relief and/or minimal improvement in signs of bleeding within approximately 8 hours after the first product infusion, but not requiring any additional FXIII-containing product for complete bleeding arrest.
Poor	No improvement or bleeding the same or worsened, other FXIII-containing product is required

**4.(iii).A.(8) Foreign phase III study in children (5.3.3.2-2, F13CD-3760 [November 2010 to January 2012])**

An open-label non-controlled study was conducted in children with congenital FXIII A-subunit deficiency aged 1 to < 6 years with a target sample size of 6 to assess the pharmacokinetics and safety of a single dose of catridecacog.

Children received a single intravenous administration of catridecacog at 35 IU/kg at a rate of  $\leq 2$  mL/min.

In this study, 6 patients received catridecacog. All patients were included in the FAS and safety analysis set. The pharmacokinetics of catridecacog was assessed for the FAS population. The results of pharmacokinetic assessment are described in "4.(ii) Summary of clinical pharmacology studies."

During the study period, 2 of 6 children (33.3%) experienced 2 adverse events (pyrexia and pain in extremity). A causal relationship with the study treatment was ruled out for both events.

None of the children experienced serious adverse events including death or adverse events resulting in discontinuation of the treatment.

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

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

No Japanese patients were enrolled in Study 1725, a pivotal phase III study to investigate the efficacy and safety of routine prophylactic treatment with catridecacog for bleeding. The efficacy and safety of routine prophylactic treatment with catridecacog for bleedings in Japanese patients were assessed in Study 3720, the extension study to Study 1725. The primary objective of Study 1725 was to assess the long-term safety of catridecacog.

After the beginning of Study 3720, the study protocol was amended to additionally assess the efficacy and safety of on-demand treatment with catridecacog for bleeding.

PMDA considers as follows:

Because of the extremely limited number of patients with congenital FXIII A-subunit deficiency, conducting a Japanese clinical study that assesses the efficacy and safety of catridecacog is difficult. No clinical trial consultations with PMDA were conducted during the development of the study design of the multi-regional Study 1725; the study was therefore conducted without the participation of Japanese patients. Study 1725 should have enrolled Japanese patients as well to obtain the efficacy and safety data of catridecacog in the Japanese population. Catridecacog and endogenous FXIII A-subunit have a similar structure, and their functions are thus considered to be similar [see "2.A.(1).4) Characterization" and "3.(i) Summary of pharmacology studies"]. This suggests that there should be little difference that may affect the evaluation of catridecacog between the Japanese and non-Japanese populations. Accordingly, the efficacy and safety of catridecacog may be evaluated based on the results of Study 3720 (Japanese patients enrolled) and Study 1725 (no Japanese patients enrolled).

The efficacy and safety data for on-demand treatment with catridecacog for bleeding should have been collected and assessed also in Study 1725, which evaluated the efficacy and safety of routine prophylactic treatment with catridecacog. However, on-demand treatment of bleeding has not been assessed. The applicant explained that there were limitations to collecting clinical data for on-demand treatment of bleeding because of the low incidence of bleeding and other reasons; this explanation is understandable [see "4.(iii).B.(2).2) Efficacy of on-demand treatment with catridecacog for bleeding"]. Data for on-demand treatment of bleeding are currently available only from Study 3720. PMDA therefore decided to evaluate the efficacy and safety of on-demand treatment of bleeding based solely on the results of Study 3720.

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

##### **4.(iii).B.(2).1) Efficacy of routine prophylactic treatment of bleeding**

###### **(a) Evaluation methods**

In Study 1725, the primary efficacy endpoint was the rate of bleeding episodes requiring treatment with a FXIII-containing product (number per patient year [yearly bleeding rate]). The endpoint was aimed to evaluate the efficacy of routine prophylactic treatment with catridecacog for bleeding. The yearly bleeding rate in the study population was to be compared with that in patients without routine prophylactic treatment (2.91 bleedings per patient year). The applicant explained how the control group in Study 1725 was selected and how the yearly bleeding rate in patients without routine prophylactic treatment (2.91 bleedings per patient year) was calculated, as described in the following sections i) and ii).

###### **i) The control group**

Patients with congenital FXIII deficiency have higher risks of serious complications associated with bleeding, and routine prophylactic treatment with a FXIII-containing product has been shown to be effective. Conducting a placebo-controlled study in this patient population thus raises ethical issues. The applicant decided to compare the study data of catridecacog with retrospectively collected historical

data. A retrospective Study F13CD-QUEST (Table 4-18) was therefore conducted to calculate the yearly bleeding rate in patients who did not receive routine prophylactic treatment with a FXIII-containing product.

**Table 4-18. Outline of Study F13CD-QUEST**

Purpose	Investigate clinical status of patients with congenital FXIII deficiency
Duration	From June to September, 2005
Countries (number of institutions)	Australia (1), Austria (1), Brazil (1), Croatia (1), Denmark (1), Germany (16), Israel (1), Poland (1), Saudi Arabia (2), Serbia and Montenegro (1), South Africa (3), Spain (2), and Switzerland (4)
Population	Patients with congenital FXIII deficiency (regardless of deficient subunit [A- or B-subunit]).

**ii) How to calculate the yearly bleeding rate in patients who did not receive routine prophylactic treatment**

In Study F13CD-QUEST, historical data were obtained from 92 patients with congenital FXIII deficiency. Among them, 23 patients did not receive routine prophylactic treatment with a FXIII-containing product. Seven patients (6 with no data on bleeding episodes and 1 treated for < 1 year) were excluded from the 23 patients. In the remaining 16 patients, the arithmetic mean of the yearly bleeding rate was calculated to be 2.91 bleedings per patient year. This value was defined as the yearly bleeding rate in patients who did not receive routine prophylactic treatment with a FXIII-containing product (Table 4-19).

**Table 4-19. Data of the patients used to calculate the yearly bleeding rate for patients treated only on-demand in Study F13CD-QUEST**

Patient	Age	Deficient subunit	Minimum FXIII activity at diagnosis (%) <sup>*1</sup>	Yearly bleeding rate (number/patient year)
a	5	Unknown	-	2.5 (2-3) <sup>*2</sup>
b	6	Unknown	8	0.5
c	10	Unknown	4	3.0
d	16	Unknown	2	11.0
e	20	Unknown	-	2.0
f	26	B	2	0.0
g	29	Unknown	21	1.5
h	31	B	55	0.0
i	33	Unknown	12	2.0
j	37	Unknown	0	2.0
k	37	Unknown	0	4.0 (2-6) <sup>*2</sup>
l	39	Unknown	50	1.0
m	46	Unknown	6	5.0
n	52	Unknown	0	12.0
o	57	A	10	0.0
p	63	A	55	0.0
N	16	—	14	16
Median (range)	32.0 (5.0-63.0)	—	6.8 (0.0-55.0)	2.0 (0.0-12.0)
Mean (standard deviation)	31.7 (17.6)	—	16.0 (21.0)	2.91 (3.7)

N = number of participants

<sup>\*1</sup> Percentage of the FXIII activity of standard plasma (1 IU/mL, calculated as 100%).

<sup>\*2</sup> Figures in parentheses are raw data obtained in Study F13CD-QUEST.

PMDA asked the applicant to provide a justification for using the data from these 16 patients to calculate the yearly bleeding rate in patients with FXIII A-subunit deficiency not treated with routine prophylactic treatment, because the 16 patients include not only those with FXIII A-subunit deficiency, the proposed indication of catridecacog, but also patients with FXIII B-subunit deficiency and those in whom deficient subunit is unknown.

The applicant responded as follows:

There are no reports showing that bleeding rate differs by the type of deficient subunit (i.e., deficiency of A-subunit, B-subunit, or both). Since patients with FXIII B-subunit deficiency account for approximately 5% of all patients with congenital FXIII deficiency (*Blood Reviews*. 2011;25:193-204), most patients in whom deficient subunit is unknown are considered to have A-subunit deficiency. Accordingly, the yearly bleeding rate of 2.91 bleedings per patient year (in patients not receiving routine prophylactic treatment with a FXIII-containing product in Study F13CD-QUEST) should be equivalent to the yearly bleeding rate in patients with FXIII A-subunit deficiency.

PMDA considered as follows:

The clinical symptoms of FXIII deficiency, i.e., bleeding tendency associated with decreased plasma FXIII activity, are similar for patients with A- subunit deficiency and those with B- subunit deficiency. The yearly bleeding rate is thus unlikely to substantially differ between the patients without routine prophylactic treatment in Study F13CD-QUEST and patients with FXIII A-subunit deficiency without routine prophylactic treatment. It is therefore acceptable to use the data from Study F13CD-QUEST as reference data of the yearly bleeding rate in patients with congenital FXIII A-subunit deficiency without routine prophylactic treatment.

On the basis of the discussion in the sections i) and ii) above, PMDA considers the method for assessing the efficacy of routine prophylactic treatment with catridecacog for bleeding, as follows:

Extremely few patients (1239 patients) have been given a diagnosis of congenital FXIII deficiency across the world (*World Federation of Hemophilia Report on the Annual Global Survey 2013*, World Federation of Hemophilia, 2014). The difficulty of conducting comparative clinical studies in this patient population is therefore understandable. Furthermore, only limited data are available for the calculation of the yearly bleeding rate in patients with FXIII A-subunit deficiency without routine prophylactic treatment. The applicant therefore had no choice but to conduct Study F13CD-QUEST and use the yearly bleeding rate obtained from Study F13CD-QUEST for the evaluation of catridecacog. However, because of the limited data obtained in Study F13CD-QUEST, the yearly bleeding rates should be assessed not only by comparison with data from Study F13CD-QUEST, but also by using other data, including literature and published reports as well as the past yearly bleeding rates in study subjects without prior routine prophylactic treatment with a conventional FXIII-containing product.



## **(b) Efficacy**

The applicant explained the efficacy of routine prophylactic treatment with catridecacog for bleeding, as follows:

In Study 1725, a low mean yearly bleeding rate (0.138 bleedings per patient year) was noted in patients receiving routine prophylactic treatment with catridecacog. Using a Poisson regression model, the yearly bleeding rate for these patients was estimated at 0.048 bleedings per patient year (95% CI, 0.0094-0.2501). The upper limit of the 95% confidence interval was <2.91 bleedings per patient year, the yearly bleeding rate in patients without routine prophylactic treatment. (The value of 2.91 was predefined as the threshold.) Thus the yearly bleeding rate in patients receiving routine prophylactic treatment with catridecacog was statistically significantly lower than the predefined threshold; this demonstrates the efficacy of catridecacog. Furthermore, the yearly bleeding rate is similar to or even lower than the yearly bleeding rate in patients receiving routine prophylactic treatment using a FXIII-containing product in Study F13CD-QUEST (mean  $\pm$  standard deviation,  $0.3 \pm 1.0$  bleedings per patient year). The mean yearly bleeding rate was also low in Study 3720 (0.042 bleedings per patient year), as in Study 1725.

Although only a limited interpretation could be made, the applicant compared the mean yearly bleeding rates in Studies 1725 and 3720 with literature data and with the number of bleeding episodes in 2 patients during the 12 months before the start of Study 1725 (who had not received routine prophylactic treatment with a FXIII-containing product before participating in Study 1725). Details are described in the following sections i) and ii).

### **i) Comparison with literature data**

Literature search revealed 3 reports on the treatment of FXIII deficiency with FXIII-containing products: (a) *Haemophilia*. 2010;16:316-21, (b) *Japanese Journal of Transfusion Medicine*. 1996;42:173-7, (c) *Thromb Res*. 2012;130S2:S12-4. Table 4-20 shows the yearly bleeding rates in the 3 reports. The mean yearly bleeding rates in Study 1725 (0.138 bleedings per patient year) and Study 3720 (0.042 bleedings per patient year) were similar to or lower than those in patients receiving routine prophylactic treatment found in literature.

**Table 4-20. Yearly bleeding rates in literature**

	Number of patients	Mean yearly bleeding rate (bleedings per year)	
		Without routine prophylactic treatment with FXIII-containing products	With routine prophylactic treatment with FXIII-containing product
(a)	7*1	2.5*3	0.2*3
(b)	4*2	4.15	0.23 (range, 0-0.4)
(c)	41*1	-	0.053*5

\*1 Patients in whom deficient subunit is unknown

\*2 Patients with FXIII A-subunit deficiency

\*3 Only spontaneous bleedings were counted

\*5 The applicant calculated the bleeding rate based on the duration of exposure and the number of bleeding episodes requiring treatment with FXIII-containing products.

**ii) Comparison with the number of bleeding episodes in 2 patients during the 12 months before the start of Study 1725 (who had not received routine prophylactic treatment with a FXIII-containing product before Study 1725)**

According to the inclusion criteria of Study 1725, 2 patients who had not received routine prophylactic treatment with a conventional FXIII-containing product before the study experienced  $\geq 2$  bleeding episodes during the 12 months before the beginning of the study. However, neither of the patients experienced bleeding events requiring treatment with a FXIII-containing product during the 52-week study period, suggesting the efficacy of routine prophylactic treatment with catridecacog.

The applicant explained the efficacy of catridecacog in Japanese patients as follows:

In Study 3720, no bleeding events requiring treatment with a FXIII-containing product occurred in 5 Japanese patients who received catridecacog for  $\geq 52$  weeks up to the cut-off date. A comparison of the mean trough plasma FXIII activity between the Japanese and overall populations revealed that the trough level was  $\geq 0.10$  IU/mL in both populations.

PMDA considers the efficacy of routine prophylactic treatment with catridecacog for bleeding as follows:

The yearly bleeding rates in the clinical studies of catridecacog should be carefully compared with those in Study F13CD-QUEST enrolling patients with different baseline characteristics, and with those from literature data in patients with different baseline characteristics who were assessed by different study conditions. The results of comparison should be carefully evaluated. Study 1725 revealed a substantially decreased yearly bleeding rate in patients receiving routine prophylactic treatment with catridecacog. In Study 3720, the yearly bleeding rate was also low as in Study 1725. None of the Japanese patients experienced bleeding episodes requiring treatment with a FXIII-containing product during the  $\geq 52$  week study period. Although data are limited, the above results on yearly bleeding rates indicate that routine prophylactic treatment with catridecacog contribute to the reduction in bleeding rate and catridecacog is expected to be effective.

#### **4.(iii).B.(2).2) Efficacy of on-demand treatment with catridecacog for bleeding**

The applicant explained the efficacy of catridecacog for the treatment of bleeding (breakthrough bleedings) that occurred during routine prophylactic treatment, as follows:

During the period up to the cut-off date in Study 3720, a single dose of catridecacog 34.7 IU/kg was administered to treat 1 episode of traumatic haemorrhage, and the bleeding stopped within 2 hours of onset. This bleeding episode occurred due to an injury of the forearm that caused intramuscular hematoma and swelling, and was considered as a moderate bleeding. The hemostatic efficacy of catridecacog at 8 hours post-dose was rated "excellent" according to the 4-rank scale.

The mechanism of action of catridecacog is similar to that of conventional plasma-derived FXIII products. Therefore, when administered for the treatment of breakthrough bleeding, catridecacog is expected to show efficacy by increasing the plasma FXIII activity, as with conventional plasma-derived FXIII products.

The number of patients with congenital FXIII A-subunit deficiency is small. Moreover, routine prophylactic treatment with a FXIII-containing product is established as a common treatment, and the incidence of breakthrough bleedings in patients receiving routine prophylactic treatment is low. Thus, it is very difficult to conduct an additional clinical study on the efficacy of a drug in the treatment of breakthrough bleedings in this population. The applicant plans to collect data on the use of catridecacog for the treatment of breakthrough bleedings in the ongoing Study 3720, the ongoing foreign post-marketing surveillance NN1841-3868 (Study 3868), and the post-marketing surveillance to be conducted in Japan.

PMDA asked the applicant to explain the efficacy and safety of on-demand treatment with catridecacog for bleeding episodes that occurred in patients without routine prophylactic treatment with catridecacog; the applicant responded as follows:

On-demand treatment with catridecacog is expected to be effective and safe regardless of whether the patient is receiving routine prophylactic treatment with catridecacog, as with plasma-derived FXIII products. However, catridecacog has never been administered to treat bleeding occurring in patients who are not receiving routine prophylactic treatment with catridecacog.

PMDA considers as follows:

The structure of catridecacog is the same as that of endogenous FXIII A-subunit. Catridecacog is therefore expected to show hemostatic effects in patients with FXIII A-subunit deficiency by functioning in a similar manner as endogenous FXIII A-subunit. To date, only 1 patient with moderate bleeding has received on-demand treatment with catridecacog. Nevertheless, the applicant's view that catridecacog is expected to be effective for the treatment of bleeding events to a certain degree is understandable. In the clinical setting, some patients may have no choice but to use catridecacog for the treatment of bleeding,

and therefore the use of catridecacog for hemostasis may be unavoidable. However, because of extremely limited data for on-demand treatment with catridecacog for bleeding, on-demand treatment with catridecacog should be administered, in principle, only to patients with no other treatment options by physicians with adequate knowledge and experience at medical institutions capable of handling emergencies appropriately. In addition, healthcare professionals should be informed of the fact that clinical data are limited and of measures to be taken in patients with a lack of hemostatic effects of catridecacog. After the market launch, data on the hemostatic effects of catridecacog should be collected appropriately.

The hemostatic effects of catridecacog is unlikely to be affected by whether a patient is receiving routine prophylactic treatment with catridecacog. Therefore on demand treatment with catridecacog need not be limited to patients receiving routine prophylactic treatment with catridecacog.

#### **4.(iii).B.(3) Safety**

The applicant explained that catridecacog is tolerable on the basis of the safety data obtained.

Separate discussions were made for the potential risk of immunogenicity, as well as the risk of shock described in the package insert for a conventional FXIII product (Fibrogammin P I.V. Injection of CSL Behring K.K.). The safety in children was also discussed.

#### **4.(iii).B.(3).1 Anti-catridecacog antibodies**

According to the submitted data, neutralizing antibodies against catridecacog have not been detected in any subjects, but anti-catridecacog non-neutralizing antibodies were detected in 1 healthy subject enrolled in Study 3788 and 4 patients with congenital FXIII A-subunit deficiency enrolled in Study 1725 (Table 4-21). The applicant explained that, as of June 3, 2014, no other subjects (than the 5 subjects listed in Table 4-21) have had anti-catridecacog antibodies in the clinical studies (Table 4-9) or in Study 3868.

**Table 4-21. Clinical course of 5 subjects with anti-catridecacog antibodies**

Subject	Age	Timing of antibody development	Study continuation/ discontinuation	Total number of exposures (as of December 31, 2013)	Neutralizing effect	Duration from the development of antibodies to the level below the detection limit (2.0)
Study 3788 (in healthy subjects)						
A	3	After the first dose of Catridecacog manufactured with Process D	Discontinued	1	Absent	Unknown (confirmed negative at 6 months after administration)
Study 1725 (in patients with congenital FXIII A-subunit deficiency)						
B	1	After the first dose	Discontinued (switched to routine prophylactic treatment with another FXIII-containing product)	2	Absent	8 months
C	1	After the first dose	Discontinued (switched to routine prophylactic treatment with another FXIII-containing product)	2	Absent	4 months
D		After the first dose	Discontinued (switched to routine prophylactic treatment with another FXIII-containing product)	3	Absent	After the second dose
E		After the second dose	Continued (treatment continued in Study 3720)	61 (13 in Study 1725 and 48 in Study 3720)	Absent	4 months

The applicant considered that anti-catridecacog non-neutralizing antibodies detected in Study 1725 are not clinically relevant for the following reasons:

- No subjects experienced allergic reactions including anaphylaxis, bleeding events requiring treatment, or change in the pharmacokinetic profile of catridecacog during the presence of antibodies or during the observation period for 4 weeks after administration.
- In all subjects, the development of antibodies was transient despite repeated exposure to catridecacog or other FXIII-containing products. (The total number of exposures in Subject E was 61 as of December 31, 2013, including 59 exposures after the detection of antibodies, but the antibodies did not reappear.)
- Administration of catridecacog after antibody development did not increase the antibody titer in any subjects.

The applicant explained the measures for patients with positive non-neutralizing anti-catridecacog antibodies, as follows:

When antibodies develop in association with the use of catridecacog, the attending physician should determine whether the treatment should be continued based on the clinical picture, the titer and nature of antibodies, and the pharmacokinetic profile of catridecacog. Data will be collected on adverse events associated with the development of anti-catridecacog antibodies in ongoing Study 3868, and post-marketing surveillance on the long-term use and pharmacovigilance activities in Japan after launch. Safety measures will be taken as needed.

PMDA considers as follows:

The submitted studies results revealed that neutralizing antibodies were not detected in any subjects. However, data to be collected from Study 3868, the post-marketing surveillance, and the pharmacovigilance activities are very important because the development of neutralizing antibodies may affect the efficacy of catridecacog.

In Study 1725, anti-catridecacog non-neutralizing antibodies were detected in 4 patients with congenital FXIII A-subunit deficiency, and 3 of the 4 patients discontinued the study due to the antibodies. The remaining 1 patient continued the study, but showed no clear effects of anti-catridecacog non-neutralizing antibodies on the pharmacokinetic profile of catridecacog. However, currently available data are extremely limited, and the effect of non-neutralizing antibodies on the pharmacokinetics of catridecacog is unclear.

Thus, when a patient shows clinically relevant changes suggesting the involvement of antibodies, such as lack of efficacy and decreased plasma FXIII activity, the patient should be tested for antibodies against catridecacog. As explained by the applicant, data on the development of antibodies should be collected after the market launch, and if necessary, should be provided appropriately and promptly to healthcare professionals.

#### **4.(iii).B.(3).2 Shock and anaphylaxis**

Shock is included in the "Clinically significant adverse reactions" section of the package insert for a conventional FXIII product (Fibrogammin P I.V. Injection of CSL Behring K.K.), but no cases of shock have been reported to date in clinical studies or foreign post-marketing surveillance of catridecacog. However, PMDA considers that precautions on shock and anaphylaxis should be provided in the package insert and other relevant documents of catridecacog similarly to those of conventional FXIII product, since catridecacog is a protein product with a potential risk of causing shock and anaphylaxis.

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

The applicant explained the safety of catridecacog in children with FXIII A-subunit deficiency as follows:

Among patients enrolled in Studies 1725 and 3720, the percentage of children with adverse events was 90.5% (19 of 21) in those aged < 18 years, and 95.7% (44 of 46) in those aged ≥ 18 years, showing no difference between the 2 age groups. The incidences of adverse drug reactions were 38.1% (8 of 21) in children aged < 18 years and 13.0% (6 of 46) in children aged ≥18 years, showing a higher incidence in the younger age group. According to the reference data from Study 3835 in children aged < 6 years, serious adverse events (2 events of head injury) were reported in 1 of the 6 children receiving catridecacog as of the cut-off date (January 15, 2013). However, a causal relationship with catridecacog therapy was ruled out for both events, and the outcome was reported as “resolved.” There were no adverse events resulting in discontinuation of the treatment.

PMDA considers as follows:

Safety profile does not clearly differ between children and adults. However, all 4 patients with anti-catridecacog antibodies in Study 1725 were aged < 18 years, and only limited data are currently available for the safety in children aged < 6 years. Safety data, including data in children, should be collected through the ongoing studies and the planned post-marketing surveillance.

According to the discussions presented in 4 (iii).B.(3) 1) to 3), catridecacog is considered to be tolerable in terms of safety because no clinically relevant adverse events were found. However, since catridecacog was evaluated only in a limited number of subjects, safety data should be appropriately collected after the market launch.

#### **4.(iii).B.(4) Clinical positioning**

PMDA's view on the clinical positioning of catridecacog is as follows:

In Japan, a plasma derived FXIII product (Fibrogammin P I.V. Injection of CSL Behring K.K.) has been approved, but there are no clinical data comparing Fibrogamin with catridecacog directly. It is thus difficult to discuss the efficacy and safety of catridecacog in relation to those of Fibrogamin. However, since catridecacog is expected to be effective and tolerable, catridecacog may be positioned as a new treatment option for patients with congenital FXIII A-subunit deficiency. Catridecacog is the first drug with clinical evidence of reducing bleeding rate by routine prophylactic treatment in patients with congenital FXIII A-subunit deficiency. However, since data for hemostatic effects of on-demand treatment with catridecacog for bleeding are extremely limited [see "4.(iii).B.(2).2) Efficacy of on-demand treatment with catridecacog for bleeding"], on-demand treatment with catridecacog should be administered, in principle, only to patients with no other treatment options by physicians with adequate knowledge and experience at medical institutions capable of handling emergencies appropriately.

Meanwhile, measures for reducing infection risks associated with source plasma are taken in the manufacturing process of plasma-derived products. The risk of infection, however, cannot be eradicated completely from plasma-derived products. On the other hand, catridecacog has no risk of causing infection because it is manufactured without using human- or animal-derived materials.

#### **4.(iii).B.(5) Indication**

The proposed indication is "control of bleeding tendency in patients with congenital blood coagulation factor XIII A-subunit deficiency."

PMDA concluded that the proposed indication is acceptable, because this allows physicians to use catridecacog for both routine prophylactic treatment of bleeding and on-demand treatment of bleeding in patients with congenital FXIII A-subunit deficiency.

#### **4.(iii).B.(6) Dosage and administration**

Proposed dosage and administration is as follows:

"The product should be reconstituted with the entire volume of the supplied solvent, and then be administered as a slow intravenous injection at a rate of  $\leq 2$  mL/min. The usual dosage of catridecacog is 35 IU/kg body weight once a month, but the dose should be adjusted appropriately according to the bleeding condition of the patient. If a bleeding episode requiring treatment occurs during prophylactic treatment with the product, an additional dose of 35 IU/kg body weight should be administered. The dose should be adjusted and additional doses should be considered as appropriate according to the patient's clinical symptoms."

##### **4.(iii).B.(6).1 Dosage regimen of routine prophylactic treatment of bleeding**

The applicant explained the rationale for the dosage regimen used in Study 1725 (35 IU/kg every 4 weeks) as follows:

There is no clear correlation between plasma FXIII activity and the frequency of bleeding. However, plasma FXIII activity of 5% to 30% (1 IU/mL represents 100%) has been reported to successfully prevent spontaneous bleeding episodes (*Haemophilia*. 2008;14:1190-200), and findings in the literature suggest that plasma FXIII activity of  $>11\%$  prevents severe bleeding episodes (*J Thromb Haemost.* 2012;10:615-21). The target minimum plasma FXIII activity should therefore be defined as 10% (0.1 IU/mL).

On the basis of the results of Studies 1661, 1662 and 1663, the mean trough plasma FXIII activity at steady state after routine prophylactic treatment with catridecacog 35 IU/kg every 28 days was expected to be approximately 10% (0.1 IU/mL) [see "4.(ii).A.(3).1 Foreign phase I clinical study"]. Accordingly, the dosage regimen in Study 1725 was set at 35 IU/kg every 4 weeks.

The dose selected for Study 1725 was fixed at 35 IU/kg with no suggestion of dose adjustment in order to avoid complexity in the assessment of efficacy and safety, since the study population to be enrolled in Study 1725 would be diverse and the incidence of bleedings requiring treatment with a FXIII-containing product, the primary endpoint, would be low.

The applicant explained the rationale for the proposed dosage regimen of routine prophylactic treatment of bleeding as follows:

Based on the dosage regimen in clinical studies of routine prophylactic treatment with catridecacog (Studies 1725 and 3720), a dose of 35 IU/kg every month was proposed as the recommended dose.

Since the mean trough plasma FXIII activity at steady state in Study 3720 was  $0.17 \pm 0.06$  IU/mL, 35 IU/kg every month would reduce the frequency of bleedings in most patients. However, a higher plasma FXIII activity may be required to control bleeding symptoms in patients with injuries and those receiving oral administration of anticoagulants or antiplatelets, (*J Thromb Haemost.* 2012;10:615-21).



Accordingly, the dose should be adjusted on the basis of the frequency of past bleeding episodes, as well as the site and severity of bleedings. In Study 1662, healthy subjects receiving catridecacog 30 IU/kg once daily for 5 consecutive days showed a plasma FXIII activity higher than the normal range but no safety concerns were identified. Therefore, there should be no problems concerning the safety of catridecacog at the time of dose adjustment.

PMDA asked the applicant to explain the relationship between plasma FXIII activity and the occurrence of bleeding in Studies 1725 and 3720, and the applicant responded as follows:

During the study period, trough plasma FXIII activity of <0.1 IU/mL was observed at some time points in some patients, but was unrelated to the occurrence of bleeding episodes requiring treatment with a FXIII-containing product. The bleeding rate was low in all patients enrolled in these studies, and favorable results were obtained in terms of efficacy and no safety concerns were found.

PMDA considers the dosage regimen of routine prophylactic treatment with catridecacog for bleeding as follows:

The dosage regimen used in Studies 1725 and 3720 did not allow physicians to adjust the dose as needed according to the condition of bleeding. The results of Studies 1725 and 3720 did not indicate any clear relationship between plasma FXIII activity and bleeding episodes. The study results also showed that routine prophylactic treatment with catridecacog may be administered safely without dose adjustment and is expected to be effective. Accordingly, it is not appropriate to recommend dose adjustment according to the condition of bleeding. The dosage regimen should be set at 35 IU/kg every 4 weeks on the basis of the regimen used in Studies 1725 and 3720.

#### **4.(iii).B.(6).2 Dosage regimen of on-demand treatment of bleeding**

The applicant explained the rationale for the dosage regimen of on-demand treatment of breakthrough bleedings, as follows:

The dose for on-demand treatment of breakthrough bleedings was set at 35 IU/kg, which has already been administered to patients as a single dose for routine prophylactic treatment. Most patients with congenital FXIII A-subunit deficiency are receiving routine prophylactic treatment with a FXIII-containing product, and therefore they experience only a limited number of bleeding episodes. Thus doses other than 35 IU/kg could not be evaluated in clinical studies.

In the clinical setting, unexpected intracranial bleeding, severe injuries associated with accidents, and other bleeding episodes may occur. In the clinical setting, therefore, the dose should be adjusted appropriately based on the patient's clinical condition and plasma FXIII activity, although no reference data on dose adjustment are available. The original proposed dosage regimen for on-demand treatment of bleeding allowed additional "as-needed" doses, but was later modified to prohibit additional doses.

PMDA considers as follows:

Since the dose of on-demand treatment with catridecacog for bleeding was not assessed, whether the proposed dose (35 IU/kg) is the optimal dose to achieve hemostasis is unknown. However, the applicant's explanation is understandable in terms of the difficulty in conducting clinical studies of catridecacog to find an optimal single dose to achieve hemostasis in this patient population. Since catridecacog 35 IU/kg is expected to increase plasma FXIII activity and thereby function as FXIII, there seems to be no choice but to select 35 IU/kg (which has already been administered to patients for bleeding prophylaxis) as the single dose of on-demand treatment of bleeding. The 35 IU/kg dose is not considered to be substantially different from the daily dose of Fibrogammin P I.V. Injection, 4.2 to 20.8 IU/kg (calculated based on the assumption that 1 mL is equivalent to 62.5 IU [see the review report of Fibrogammin P I.V. Injection dated August 8, 2013 (in Japanese only)] and patient body weight is 60 kg).

The protocol of Study 3720, in which 1 patient received on-demand treatment of bleeding, did not allow dose adjustment according to clinical condition and plasma FXIII activity, nor did it specify the clinical conditions requiring dose adjustment or target plasma FXIII activity. Accordingly, adjusting the dose as needed should not be recommended. Since data for on-demand treatment with catridecacog for bleeding are extremely limited [see "4.(iii).B.(2).2 Efficacy of on-demand treatment with catridecacog for bleeding"], the following precautions should be provided concerning on-demand treatment with catridecacog for bleeding: (1) catridecacog should be administered, in principle, only to patients with no other treatment options by physicians with adequate knowledge and experience at medical institutions capable of handling emergencies appropriately; (2) only a single dose of catridecacog may be administered for on-demand treatment of bleeding, and treatment should be switched to other therapy in patients with insufficient response to catridecacog.

Catridecacog has never been used to treat bleeding in patients not receiving routine prophylactic treatment with catridecacog. The proposed dosage regimen for the treatment of breakthrough bleedings may be used for the treatment of bleeding in such patients.

#### **4.(iii).B.(6).3 Rate of injection**

The applicant explained the rate of injection as follows.

In Studies 1725 and 3720, catridecacog was administered as a slow intravenous injection at a rate of  $\leq 2$  mL/min, revealing no safety concerns. Accordingly, the applicant proposed the following wording for dosage and administration: "administered as a slow intravenous injection at a rate of  $\leq 2$  mL/min."

PMDA accepted the applicant's explanation.

On the basis of the above reviews presented in 4.(iii).B.(6).1 to 3), PMDA concluded that the "dosage and administration" and "precautions for dosage and administration" should be described as follows:

[Dosage and administration]

The product should be reconstituted with the entire volume of the supplied solvent, and then be administered as a slow intravenous injection at a rate of  $\leq 2$  mL/min.

The usual single dose of catridecacog is 35 IU per 1 kg body weight.

For routine prophylactic treatment, catridecacog 35 IU/kg body weight should be administered every 4 weeks.

[Precautions for dosage and administration]

- For on-demand treatment of bleeding, the product should be administered, in principle, only to patients with no other treatment options by physicians with adequate knowledge and experience at medical institutions capable of handling emergencies appropriately.
- For on-demand treatment of bleeding, only a single dose of the product may be administered. Treatment should be switched to other therapy in patients with insufficient response to the product.

#### **4.(iii).B.(7) Post-marketing investigations**

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

The applicant plans to conduct a use-results survey to collect data on the safety and efficacy of long-term treatment with catridecacog. To collect extensive safety data on catridecacog, the survey covers all Japanese patients receiving catridecacog with an 8-year registration period and a 9-year survey period. In 2013, a survey was conducted to determine the required amounts of blood coagulation factor products, revealing that 37 of 52 patients (72%) with FXIII deficiency or abnormality were treated with FXIII products (Blood Products Research Organization. *The Blood Products Research Organization Newsletter*. 2013;138). If approximately 10% of them switch their treatment to catridecacog and 4 patients enrolled in Study 3720 continue to use catridecacog, approximately 8 patients are assumed to be included in the use-results survey.

PMDA considers as follows:

An extremely small number of Japanese patients enrolled in the clinical studies of catridecacog, and clinical experience with catridecacog is limited in Japan. Therefore, in the post-marketing surveillance, safety data should be collected as much as possible not only from patients receiving long-term catridecacog therapy but also from other patients using catridecacog in the clinical setting. Obtained information should be provided promptly to healthcare professionals. The post-marketing surveillance should cover all Japanese patients receiving catridecacog, wherever possible, and should be continued for a certain period of time.

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

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

Document based GLP/GCP inspection is currently undergoing. The results and PMDA's conclusion will be reported in Review Report (2).

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

GCP on-site inspection is currently undergoing. The results and PMDA's conclusion will be reported in Review Report (2).

### **IV. Overall evaluation**

Based on the data submitted by the applicant, PMDA has concluded that catridecacog is expected to be effective in controlling bleeding tendency in patients with congenital coagulation factor XIII A-subunit deficiency, and that its safety is acceptable in view of its observed benefits. PMDA considers that catridecacog is clinically meaningful as a therapeutic option to control bleeding tendency in patients with congenital FXIII A-subunit deficiency.

PMDA considers that catridecacog may be approved if the drug is not considered to have any particular problem based on the review by Expert Discussion on issues including the efficacy, safety, and post-marketing surveillance of catridecacog.

## Review Report (2)

February 16, 2015

### I. Product Submitted for Registration

[Brand name]	NovoThirteen 2500 IU for Intravenous Injection 2500
[Non-proprietary name]	Catridecacog (Genetical Recombination)
[Applicant]	Novo Nordisk Pharma Ltd.
[Date of application]	August 29, 2014

### II. Content of the Review

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

#### (1) Efficacy

##### 1) Efficacy of routine prophylactic treatment of bleeding

PMDA’s conclusion:

In Study F13CD-1725 (Study 1725) and Study F13CD-3720 (Study 3720), the efficacy of catridecacog was assessed with the rate of bleeding episodes requiring treatment with a FXIII-containing product (number per patient year) in the duration of catridecacog therapy. The mean yearly bleeding rate in Study 1725 was 0.138 bleedings per patient year, and the age-adjusted rate was 0.048 per patient year (95% CI: 0.0094-0.2501). The upper limit of the 95% confidence interval was <2.91 per patient year, the predefined threshold. The yearly bleeding rate in patients receiving routine prophylactic treatment with catridecacog was statistically significantly lower than the predefined threshold. In Study 3720, the extension study to Study 1725, the mean yearly bleeding rate was as low as 0.042 bleedings per patient year. Routine prophylactic treatment with catridecacog is thus considered to contribute to the reduction in bleeding rate and is expected to be effective.

This conclusion was supported by the expert advisors.

##### 2) Efficacy of on-demand treatment of bleeding

PMDA’s conclusion:

In Study 3720, hemostatic efficacy was assessed with a 4-rank scale [see Table 4-17 in Review Report (1)]. Catridecacog was administered to treat 1 episode of moderate bleeding, and the hemostatic efficacy

was rated "excellent." Since the structure of catridecacog is the same as that of endogenous FXIII A-subunit, catridecacog is expected to show hemostatic effects with a mechanism of action similar to that of endogenous FXIII A-subunit. In the clinical setting, there may be situations where a patient has no choice but to use catridecacog (e.g., a long time is required to prepare or obtain a conventional FXIII product). Catridecacog may therefore be used for on-demand treatment of bleeding regardless of whether the patient is receiving routine prophylactic treatment with catridecacog.

This conclusion was supported by the expert advisors.

## **(2) Safety**

PMDA's conclusion:

Catridecacog is considered to be tolerable on the basis of the submitted data. However, catridecacog is a protein product with a potential risk of causing shock and anaphylaxis. Patients and healthcare professionals should therefore be cautioned against shock and anaphylaxis through the package insert and other relevant documents, in a similar manner as for conventional FXIII products.

When clinically relevant changes suggesting the involvement of antibodies is observed, such as lack of efficacy and decreased plasma FXIII activity, the patient should be tested for antibodies in plasma. Information obtained after the market launch should be provided appropriately and promptly to health professionals.

This conclusion was supported by the expert advisors.

## **(3) Clinical positioning**

PMDA's conclusion:

Based on the results of clinical studies, catridecacog may be positioned as a new treatment option for patients with congenital FXIII A-subunit deficiency. Catridecacog is the first drug with clinical evidence of reducing bleeding rate by routine prophylactic treatment in patients with congenital FXIII A-subunit deficiency. However, since data for hemostatic effects of on-demand treatment with catridecacog for bleeding are extremely limited, on-demand treatment with catridecacog should be administered, in principle, only to patients with no other treatment options by physicians with adequate knowledge and experience at medical institutions capable of handling emergencies appropriately.

Catridecacog has no risk of causing infection because it is manufactured without using human- or animal-derived materials.

This conclusion was supported by the expert advisors.

#### **(4) Indication**

PMDA concluded that the indication of "control of bleeding tendency in patients with congenital blood coagulation factor XIII A-subunit deficiency" is acceptable because this allows physicians to use catridecacog for both routine prophylactic treatment of bleeding and on-demand treatment of bleeding in patients with congenital FXIII A-subunit deficiency.

This conclusion was supported by the expert advisors.

#### **(5) Dosage and administration**

##### **1) Dosage and administration of routine prophylactic treatment of bleeding**

PMDA's conclusion:

The dosage regimen for Studies 1725 and 3720 was selected to achieve steady-state trough plasma FXIII activity of 0.1 IU/mL. The dosage and administration of catridecacog should be 35 IU/kg every 4 weeks, as per Studies 1725 and 3720.

The proposed dosage and administration allowed physicians to adjust the dose according to the bleeding condition of the patient. However, there have been no results of clinical studies where the dose of catridecacog was adjusted according to the bleeding condition of the patient. No clear relationship between plasma FXIII activity and bleeding episodes has been found. The clinical study results show that routine prophylactic treatment with catridecacog may be administered safely without dose adjustment and is expected to be effective. Accordingly, it is not appropriate to recommend dose adjustment according to the condition of bleedings.

This conclusion was supported by the expert advisors.

Some expert advisors made the following comments:

The explanation that no substantial ethnic differences have been found in the efficacy and pharmacokinetic profile of catridecacog is understandable. In addition, it is desirable to specify that catridecacog therapy ensures the target plasma FXIII activity of  $\geq 0.1$  IU/mL in Japanese patients as in non-Japanese patients [see Table 4-7 in Review Report (1)].

PMDA explained as follows:

In Study 3720, baseline plasma FXIII activity was determined in all subjects including 5 Japanese subjects to obtain data on trough levels. The mean trough plasma FXIII activity was  $0.18 \pm 0.04$  IU/mL in all 60 patients receiving catridecacog and  $0.16 \pm 0.02$  IU/mL in the 5 Japanese patients. This indicates similar trough FXIII activity for non-Japanese and Japanese patients.

##### **2) Dosage and administration of on-demand treatment of bleeding**

PMDA's conclusion:

Conducting a clinical study to investigate the hemostatic effect of catridecacog is difficult, and catridecacog 35 IU/kg is expected to increase plasma FXIII activity and thereby function as FXIII. Selecting 35 IU/kg (which has been administered to patients to prevent bleeding episodes) as the dose for on-demand treatment of bleeding is acceptable.

Meanwhile, the protocol of Study 3720 did not allow investigators to adjust the dose as needed, nor did it specify the criteria of clinical conditions requiring dose adjustment nor determine the target plasma FXIII activity. Therefore adjusting dose as needed should not be recommended.

Since data on the hemostatic effect of catridecacog are very limited, (1) physicians should consider other treatment options before using catridecacog, and (2) on-demand treatment with catridecacog should be used only in unavoidable situations (e.g., long time is required to prepare or obtain a conventional FXIII product) by physicians with adequate knowledge and experience at medical institutions capable of handling emergencies appropriately. Moreover, healthcare professionals should be advised to administer only a single dose of catridecacog for on-demand treatment of bleeding, and to switch treatment to other therapy in patients with insufficient response to catridecacog.

The expert advisors commented that since catridecacog has a long elimination half-life [see Table 4-7 in Review Report (1)], and adverse drug reactions may persist if developed, the dose should not be increased without careful consideration. The above conclusion of PMDA was supported by the expert advisors.

### **3) Rate of injection**

PMDA concluded that the proposed wording for dosage and administration (i.e., "administered as a slow intravenous injection at a rate of  $\leq 2$  mL/min") is acceptable, as per the protocols of Studies 1725 and 3720.

This conclusion was supported by the expert advisors.

On the basis of the Expert Discussion regarding the above sections 1) to 3), and that catridecacog will be used mainly as routine prophylactic treatment, PMDA concluded that the wording for dosage and administration should be modified as below, and that the package insert should instruct readers to see the "Clinical Results" so that healthcare professionals are aware of limited clinical experience of on-demand treatment with catridecacog for bleeding. Accordingly, PMDA asked the applicant to modify the proposed dosage and administration and the relevant sections in the package insert; the applicant responded appropriately.



[Dosage and administration]

The product should be reconstituted with the entire volume of the supplied solvent, and then be administered as a slow intravenous injection at a rate of  $\leq 2$  mL/min.

The recommended dosage of catridecacog for routine prophylaxis is 35 IU/kg body weight every 4 weeks.

A single dose of catridecacog 35 IU/kg body weight may be administered for on-demand treatment of bleeding.

[Precautions for dosage and administration]

- For on-demand treatment of bleeding, other treatment options should be well considered before catridecacog is administered. In situations where the use of catridecacog is unavoidable, catridecacog should be administered by physicians with adequate knowledge and experience at medical institutions capable of handling emergencies appropriately.
- For on-demand treatment of bleeding, only a single dose catridecacog should be administered. Treatment should be switched to other therapy in patients with insufficient response to catridecacog. (Clinical experience of on-demand treatment of bleeding is limited [see the "Clinical Results" section]).

**(5) The proposed risk management plan**

On the basis of the review in Section "4.(iii).B.(7) Post-marketing investigations" in the Review Report (1), PMDA concluded that (1) post-marketing surveillance should be conducted to collect safety data as much as possible not only from patients receiving long-term catridecacog therapy but also from other patients using catridecacog, and obtained information should be provided promptly to healthcare professionals, and that (2) the surveillance should cover all Japanese patients receiving catridecacog, wherever possible, and should be continued for a certain period of time.

This conclusion was supported by the expert advisors. Some expert advisors commented that since efficacy data including the hemostatic effect of catridecacog are important, efficacy data including patient characteristics should be collected as much as possible.

PMDA communicated these comments to the applicant, and the applicant responded that it would address this matter appropriately.

PMDA concluded that the proposed risk management plan should include the safety and efficacy specifications listed in Table 1, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities listed in Tables 2 and 3.

**Table 1. Safety and efficacy specifications in the proposed risk management plan**

Safety Specification		
Important identified risks	Important potential risks	Important missing information
None	Development of neutralizing antibodies Shock and anaphylaxis Thromboembolic events	None
Efficacy Specifications		
Effectiveness in the clinical setting		

**Table 2. Outline of additional pharmacovigilance activities, and additional risk minimization activities in the proposed risk management plan**

Additional pharmacovigilance activities	Additional risk minimization activities
Early post-marketing phase vigilance Use-results survey Post-marketing clinical study* <sup>1</sup>	Early post-marketing phase vigilance

\*<sup>1</sup> After marketing authorization, the ongoing Study 3720 will be continued as a post-marketing clinical study until catridecacog will be commercially available in medical institutions.

**Table 3. Outline of the proposed drug use-results survey**

Purpose	Assessment of the safety and efficacy of catridecacog in the clinical setting
Survey method	All-case surveillance
Population	All Japanese patients receiving catridecacog
Observation period	Up to 9 years for each patient
Planned number of patients	All Japanese patients receiving catridecacog
Major survey items	- Development of anti-catridecacog antibodies, allergic reactions, thromboembolic events, and insufficient efficacy - Causes of bleeding, site of bleeding, drugs used to treat bleeding, outcome of the treatment.

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

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

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

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

GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.2-1). As a result, PMDA concluded that there should be no major problems with conducting a regulatory review based on the submitted application documents.

#### IV. Overall Evaluation

As a result of the above review, PMDA concludes that the product may be approved with the following conditions for approval, indication, and dosage and administration, as shown below. Since catridecacog is an orphan drug, the re-examination period is 10 years. Neither the drug substance nor the drug product is classified as a poisonous drug or a powerful drug. The product is not classified as a biological product or a specified biological product.

[Indication]	Control of bleeding tendency in patients with congenital blood coagulation factor XIII A-subunit deficiency
[Dosage and administration]	<p>The product should be reconstituted with the entire volume of the supplied solvent, and then be administered as a slow intravenous injection at a rate of <math>\leq 2</math> mL/min.</p> <p>The recommended dosage of catridecacog for routine prophylaxis is 35 IU/kg body weight every 4 weeks.</p> <p>A single dose of catridecacog 35 IU/kg body weight may be administered for on-demand treatment of bleeding.</p>
[Conditions for approval]	<p>The applicant is required to</p> <ul style="list-style-type: none"><li>• Develop and appropriately implement a risk management plan.</li><li>• Conduct a use-results survey that should cover all Japanese patients receiving the product, to identify the characteristics of patients receiving the product, to collect efficacy and safety data, and to take appropriate measures to ensure the proper use of the product, wherever possible, since the number of subjects enrolled in the Japanese clinical studies of the product is extremely limited.</li></ul> <p>The survey should be continued for a certain period of time.</p>