

Review Report

August 7, 2025

Pharmaceuticals and Medical Devices Agency

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

Brand Name	Jivi for IV Injection 500 Jivi for IV Injection 1000 Jivi for IV Injection 2000 Jivi for IV Injection 3000
Non-proprietary Name	Damoctocog Alfa Pegol (Genetical Recombination) (JAN*)
Applicant	Bayer Yakuhin, Ltd.
Date of Application	October 30, 2024
Dosage Form/Strength	Lyophilized powder for reconstitution for injection: Each vial contains 500, 1000, 2000, or 3000 IU Damoctocog Alfa Pegol (Genetical Recombination).
Application Classification	Prescription drug, (6) Drug with a new dosage
Items Warranting Special Mention	None
Reviewing Office	Office of Vaccines and Blood Products

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in controlling bleeding tendency in patients aged ≥ 7 and < 12 years with blood coagulation factor VIII deficiency, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following condition.

Indication

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

(No change)

This English translation of this Japanese review report is intended to serve as reference material made available for the convenience of users. In the event of any inconsistency between the Japanese original and this English translation, the Japanese original shall take precedence. PMDA will not be responsible for any consequence resulting from the use of this reference English translation.

Dosage and Administration

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

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

For patients aged ≥ 12 years, the usual regimen for routine prophylaxis is 30 to 40 IU/kg body weight twice weekly. The regimen may be adjusted to 45 to 60 IU/kg body weight every 5 days or 60 IU/kg body weight once weekly, according to the patient's condition. For children aged ≥ 7 and < 12 years, the usual regimen for routine prophylaxis is 40 to 60 IU/kg body weight twice weekly.

(Underline denotes additions. Strikethrough denotes deletions.)

Approval Condition

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

**Japanese Accepted Name (modified INN)*

Review Report (1)

July 2, 2025

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

Product Submitted for Approval

Brand Name	Jivi for IV Injection 500
	Jivi for IV Injection 1000
	Jivi for IV Injection 2000
	Jivi for IV Injection 3000
Non-proprietary Name	Damoctocog Alfa Pegol (Genetical Recombination)
Applicant	Bayer Yakuhin, Ltd.
Date of Application	October 30, 2024
Dosage Form/Strength	Lyophilized powder for reconstitution for injection: Each vial contains 500, 1000, 2000, or 3000 IU Damoctocog Alfa Pegol (Genetical Recombination).

Proposed Indication

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

(No change)

Proposed Dosage and Administration

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

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

For patients aged ≥12 years, the usual regimen for routine prophylaxis is 30 to 40 IU/kg body weight twice weekly. The regimen may be adjusted to 45 to 60 IU/kg body weight every 5 days or 60 IU/kg body weight once weekly, according to the patient's condition. For children aged ≥7 and <12 years, the usual regimen for routine prophylaxis is 40 to 60 IU/kg body weight twice weekly.

(Underline denotes changes.)

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List of Abbreviations

See Appendix.

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

Hemophilia A (congenital factor VIII deficiency) is a bleeding disorder caused by a deficiency or dysfunction of coagulation factor VIII (FVIII) and may cause serious bleeding symptoms. Conventional treatments for patients with hemophilia A focus on bleeding control. In addition to FVIII replacement therapy for on-demand treatment and control of bleeding, regular replacement therapy with drugs targeting FVIII and tissue factor pathway inhibitor (TFPI) is performed mainly for patients with severe hemophilia A, aiming to reduce the frequency of bleeding episodes (control of bleeding tendency). In Japan, approved FVIII-targeted drugs include multiple human plasma-derived and recombinant FVIII products as well as emicizumab, which are monoclonal antibodies that bind to activated coagulation factor IX (FIXa) and coagulation factor X (FX) and substitute for the cofactor function of FVIII, and approved TFPI-targeted drugs include concizumab and marstacimab, which are monoclonal antibodies that inhibit TFPI.

Damoctocog Alfa Pegol (Genetical Recombination) (hereinafter referred to as damoctocog alfa pegol) is a polyethylene glycolated (PEGylated) recombinant FVIII product bound to PEG to prolong its plasma half-life. It was approved in September 2018 for the indication of “control of bleeding tendency in patients with blood coagulation factor VIII deficiency” and the dosage and administration for use in patients with hemophilia A aged ≥ 12 years.

Based on the results of a foreign phase III study in patients with hemophilia A aged ≥ 7 and < 12 years (Study 21824) and a foreign phase III study in patients with hemophilia A aged < 12 years (Study 15912), the applicant has submitted a partial change application for damoctocog alfa pegol to add dosage and administration for patients aged ≥ 7 and < 12 years. As of May 2025, damoctocog alfa pegol is approved in at least 50 countries or regions, including the US and Europe, and approval for use in patients aged ≥ 7 and < 12 years has been granted in the US.

2. Quality and Outline of the Review Conducted by PMDA

The present application is intended for a new dosage. Therefore, no data relating to quality were submitted.

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

Although the present application is intended for a new dosage, no new data were submitted because non-clinical pharmacology data were considered to have been evaluated during the review process for the initial approval of damoctocog alfa pegol.

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

Although the present application intended for a new dosage, no new data were submitted because non-clinical pharmacokinetics data were considered to have been evaluated during the review process for the initial approval of damoctocog alfa pegol.

5. Toxicology and Outline of the Review Conducted by PMDA

The present application is intended for a new dosage. Therefore, no toxicology data were submitted.

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

6.1 Biopharmaceutic studies and associated analytical methods

Although the present application is intended for a new dosage, no new data were submitted because the data related to biopharmaceutic studies and associated analytical methods were considered to have been evaluated during the review process for the initial approval of damoctocog alfa pegol.

6.2 Clinical pharmacology

As clinical pharmacology data, the applicant submitted the results of re-analysis of the data from the foreign phase III study (CTD 5.3.5.2.5 at the initial approval, Study 15912 [main study]) after re-stratifying the patients into the age categories of “<7 years” and “≥7 and <12 years,” though they had been divided to <6 years” and “≥6 and <12 years.

6.2.1 Study in patients

6.2.1.1 Foreign phase III study (CTD 5.3.5.2.5 at the initial approval, Study 15912 [main study]; Study period, May 2013 to March 2015)

The pharmacokinetics of damoctocog alfa pegol was evaluated in 34 patients with severe hemophilia A (FVIII activity level <1%) aged <12 years (18 patients aged <7 years, 16 patients aged ≥7 and <12 years) who had been previously treated for >50 exposure days with any FVIII concentrate and had no history or current evidence of inhibitors. Following a single intravenous dose of damoctocog alfa pegol 60 IU/kg, plasma FVIII activity was measured at ≥4 time points (at pre-dose and 20-30 minutes and 72 hours post-dose). Pharmacokinetic parameters are shown in Table 1. Compared with patients aged <7 years, patients aged ≥7 and <12 years had an approximately 34% higher AUC, with a slightly higher C_{max} and a slightly longer t_{1/2}.

Table 1. Pharmacokinetic parameters in patients aged <12 years (geometric mean [CV%])^{a)}

	<7 years (N = 15 ^{b)})	≥7 and <12 years (N = 12 ^{c)})
AUC (IU·h/dL)	2120 (38.1)	2840 (20.3)
C _{max} (IU/dL)	118 (17.9) ^{d)}	128 (19.9) ^{e)}
t _{1/2} (h)	14.6 (27.5)	15.6 (23.5) ^{f)}
MRT (h)	20.0 (26.6)	23.5 (24.4)
CL (dL/h/kg)	0.0285 (39.3)	0.0211 (19.6)
V _{ss} (dL/kg)	0.569 (24.9)	0.496 (20.2)

a) Plasma FVIII activity was determined by chromogenic substrate assay (lower limit of quantification, 1.5 IU/dL).

b) Excluding 1 patient with a protocol deviation due to dose error, 1 patient with an outlier (due to low exposure), and 1 patient in whom only C_{max} was evaluable.

c) Excluding 1 patient with a protocol deviation due to dose error, 2 patients in whom only t_{1/2} was evaluable, and 1 patient in whom C_{max} was evaluable.

d) Including 1 patient in whom only C_{max} was evaluable (N = 16).

e) Including 1 patient in whom only C_{max} was evaluable (N = 13).

f) Including 2 patients in whom only t_{1/2} was evaluable (N = 14).

6.R Outline of the review conducted by PMDA

The applicant’s explanation about the pharmacokinetics of damoctocog alfa pegol in patients with hemophilia A aged ≥7 and <12 years:

The arithmetic mean ± standard deviation (SD) of half-life of damoctocog alfa pegol was 16.0 ± 3.6 hours in patients aged ≥7 and <12 years in Study 15912 (main study). The value was longer than that observed for existing standard half-life FVIII products (12.0 ± 2.1 hours [≥6 and <12 years] for

KOVALTRY,¹⁾ 10.9 ± 1.6 hours [≥ 5 and < 12 years] for ADVATE²⁾), though no direct comparison with the existing product was performed. A higher CL and a shorter $t_{1/2}$ were observed in patients aged ≥ 7 and < 12 years in Study 15912 (main study), compared with the pharmacokinetic parameters of patients aged ≥ 12 years³⁾ that had been obtained in the clinical studies of damoctocog alfa pegol (Studies 13401 and 13024) and evaluated for the initial approval.

It is therefore reasonable, from a pharmacokinetic point of view, to administer damoctocog alfa pegol as prophylactic treatment twice weekly, at a dose of 40 to 60 IU/kg for patients aged ≥ 7 and < 12 years, which is slightly higher than the dose of 30 to 40 IU/kg for patients aged ≥ 12 years.

PMDA's view:

The applicant's explanation is acceptable. However, the appropriateness of the dosage regimen for patients aged ≥ 7 and < 12 years should be discussed, including the dosage regimens specified in Study 15912 and Study 21824 which was conducted in patients with hemophilia A aged ≥ 7 to < 12 years [see Section 7.1] as well as efficacy and safety results. These issues will be discussed in Section 7.R.4.

In addition, anti-drug antibodies (ADAs), including anti-damoctocog alfa pegol antibodies, anti-PEG antibodies, and anti-PEG immunoglobulin M [IgM] antibodies, will be discussed in Section 7.R.3.1.

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

The applicant submitted efficacy and safety evaluation data, in the form of results data from 2 foreign phase III studies (CTD 5.3.5.2.1, Study 21824 [main study]; CTD 5.3.5.2.2, Study 15912 [extension phase]), and the results of a foreign phase III study (CTD 5.3.5.2.5 for the initial approval, Study 15912 [main study]) as reference data. Table 2 shows a list of clinical studies. The applicant also submitted the results of a pooled analysis of 2 foreign phase III studies (Study 15912 [main study] and Study 21824 [main study]) (CTD 5.3.5.3.1) as evaluation data [see Sections 7.R.2.1 to 3 and 7.R.3.1].

¹⁾ US labeling (<https://www.fda.gov/media/96215/download?attachment>)

²⁾ US labeling (<https://www.fda.gov/media/70008/download>)

³⁾ See Section 6.2 of the "Review Report for Jivi for IV Injection 250, Jivi for IV Injection 500, Jivi for IV Injection 1000, Jivi for IV Injection 2000, Jivi for IV Injection 3000, dated August 2, 2018."

Table 2. List of clinical studies

Data category	Location	Study identifier	Phase	Study population	No. of subjects treated	Dosage regimen	Main endpoints
Evaluation	Foreign	21824 (main study)	III	Previously treated patients with severe hemophilia A (≥ 7 and < 12 years)	35 subjects	Intravenous administration of damoctocog alfa pegol 40 IU/kg (dose increase permitted up to 60 IU/kg) twice weekly ^{a)} for ≥ 50 exposure days and for ≥ 6 months	Safety Efficacy
	Foreign	15912 (extension phase)	III	Subjects completing the main study or Part 2 ^{b)} of Study 15912	59 subjects (32 subjects aged < 6 years, 27 subjects aged ≥ 6 and < 12 years)	Intravenous administration of damoctocog alfa pegol 25-60 IU/kg twice weekly, 45-60 IU/kg every 5 days, or 60 IU/kg every 7 days at the investigator's discretion for ≥ 100 exposure days in total in the main study or Part 2	Safety Efficacy
Reference	Foreign	15912 (main study)	III	Previously treated patients with severe hemophilia A (≥ 0 and < 12 years)	61 subjects (32 subjects aged < 6 years, 29 subjects aged ≥ 6 and < 12 years), including 25 subjects aged ≥ 7 and < 12 years as the population for the present application	Intravenous administration of damoctocog alfa pegol 25-60 IU/kg twice weekly, 45-60 IU/kg every 5 days, or 60 IU/kg every 7 days at the investigator's discretion for ≥ 50 exposure days and for ≥ 6 months	Safety Efficacy Pharmacokinetics

a) In Study 15912, damoctocog alfa pegol was to be administered twice weekly, every 5 days, or every 7 days, but most subjects received damoctocog alfa pegol twice weekly or every 5 days at the investigator's discretion. In Study 21824, therefore, twice-weekly dosing was evaluated in the main study and not only twice-weekly dosing but also every-5-day dosing was allowed in the ongoing extension phase.

b) Previously treated patients with severe hemophilia A aged < 6 years received damoctocog alfa pegol 25 to 60 IU/kg twice weekly for 12 weeks (CTD 5.3.5.2.7 for the initial approval).

The clinical studies are summarized in the subsections below. The results of Study 15912 (main study),⁴⁾ which had been already evaluated for the initial approval, are not reported, and only the results of the extension phase are included in this report. The results of pharmacokinetic evaluation in subjects aged ≥ 7 and < 12 years in Study 15912 (main study) are described in Section “6.2 Clinical pharmacology.”

7.1 Foreign phase III study (CTD 5.3.5.2.1, Study 21824 [main study]; Study period, March 2022 to January 2024)

An open-label, uncontrolled study was conducted to evaluate the safety and efficacy of damoctocog alfa pegol in male children aged ≥ 7 and < 12 years with severe hemophilia A (FVIII activity level $< 1\%$) who had been previously treated for ≥ 50 exposure days with any FVIII concentrate and had no history or current evidence of inhibitors (target sample size, 30 subjects⁵⁾) at 17 study sites in 7 foreign countries.

This study was designed similarly to Study 15912 (main study) because it was planned on the assumption that the incidence of adverse events of special interest (AESI) (hypersensitivity reactions and loss of efficacy associated with anti-PEG antibodies) leading to treatment discontinuation or

⁴⁾ See Section 7.3.1 of the “Review Report for Jivi for IV Injection 250, Jivi for IV Injection 500, Jivi for IV Injection 1000, Jivi for IV Injection 2000, Jivi for IV Injection 3000 dated August 2, 2018.”

⁵⁾ The target sample size for this study was determined on the assumption that the primary endpoint of incidence of AESI would be analyzed using the Bayesian method based on pooled data from this study and Study 15912 (25 subjects aged ≥ 7 and < 12 years). Based on neutral beta (1/4, 1/4) prior distribution, the incidence of AESI was assumed to follow a beta binomial distribution. Assuming that AESI occurred in $< 5\%$ of 30 subjects enrolled in this study, pooled analysis would provide a posterior probability of greater than 90% that the true incidence of AESI would be $< 5\%$.

interruption was analyzed based on pooled data from subjects in this study and 25 subjects aged ≥ 7 and < 12 years in the completed Study 15912 (main study)⁴⁾ [see Section 7.R.1].

Subjects received intravenous infusion of damoctocog alfa pegol at 40 IU/kg twice weekly as prophylactic treatment. The dose was allowed to be increased up to 60 IU/kg for each subject based on activity level, previous treatment, etc. at the investigator's discretion at any time during the study period. The treatment was to be continued for ≥ 6 months and ≥ 50 exposure days.

A total of 35 subjects were enrolled in the study and received at least 1 dose of damoctocog alfa pegol, and all of them were included in the safety analysis set (SAF). Of them, 32 subjects were included in the modified intent-to-treat (mITT) population, which was used as the primary efficacy analysis set. The remaining 3 enrolled subjects who had no treatment or bleeding data in the electronic patient diary or who were treated but had < 3 months treatment or bleeding data in the electronic patient diary were excluded from analysis.

The number of damoctocog alfa pegol exposure days per subject (mean $\pm$ SD [range]) was 48.9 ± 14.2 [1, 59] days in the SAF and 53.0 ± 4.0 [35, 59] days in the mITT population. In both populations, 31 subjects (88.6% and 96.9%, respectively) achieved ≥ 50 exposure days.

The primary endpoint of the study was AESIs occurring during the first 4 exposure days, and an AESI of loss of efficacy due to high-titer (1:64) anti-PEG IgM antibodies was reported in 1 subject. In this subject, study drug administration was interrupted and restarted after the antibodies had disappeared.

Adverse events were reported in 60% (21 of 35) of subjects between the first dose and 7 days after the last dose of damoctocog alfa pegol. All of the reported adverse events were mild or moderate in severity. Adverse events reported in $\geq 5\%$ of subjects are shown in Table 3.

Table 3. Adverse events reported in $\geq 5\%$ of subjects (Study 21824 [main study], SAF [N = 35])

Event	No. of subjects (%)
Cough	4 (11.4)
Pyrexia	3 (8.6)
Influenza	3 (8.6)
Headache	3 (8.6)
Abdominal pain	2 (5.7)
Nasopharyngitis	2 (5.7)
Sinusitis	2 (5.7)
Viral pharyngitis	2 (5.7)
Pain in extremity	2 (5.7)

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A total of 5 study drug-related adverse events were reported in 3 subjects (8.6%), which included drug ineffective (1 event), infusion site pain (3 events), and injection site pruritus (1 event) in 1 subject (2.9%) each. All of these events had resolved, with the exception of infusion site pain, at the end of the main study.

One serious adverse event of abdominal pain was reported in 1 subject (2.9%), which resolved and was assessed as unrelated to the study drug. No adverse events leading to discontinuation of the study drug or deaths were reported.

As for efficacy, the median annualized bleeding rates (ABR)⁶⁾ [range] for bleeds requiring treatment and total bleeds in the main study were 0.00 [0.0, 10.4] bleeds/year and 0.92 [0.0, 49.5⁷⁾] bleeds/year, respectively. The hemostatic efficacy for bleeds requiring treatment (21 events) was rated as “excellent” or “good” in 71.4% (15 of 21) of the bleeding events by subjects or their parents (caregivers) according to the criteria shown in Table 4.

Table 4. Subject-reported assessment of response to treatment of a bleed

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

7.2 Foreign phase III study (CTD 5.3.5.2.2, Study 15912 [extension phase]; Study period, March 2014 to February 2020)

An uncontrolled, extension study was conducted to evaluate the long-term safety and efficacy of damoctocog alfa pegol in male children aged <12 years with severe hemophilia A (FVIII activity level <1%) who had been previously treated for ≥50 exposure days with any FVIII concentrate, had no history or current evidence of inhibitors, had completed either the main study or Part 2 of Study 15912, and provide consent to participate in the extension phase at 32 study sites in 14 foreign countries.

Subjects received intravenous infusion of damoctocog alfa pegol at 25 to 60 IU/kg twice weekly as prophylactic treatment, 45 to 60 IU/kg every 5 days, or 60 IU/kg every 7 days, according to the clinical needs of each subject based on activity level, previous bleeding episodes, etc. The dosing interval and dose were allowed to be changed at any time. The treatment was continued for the cumulative number of ≥100 exposure days for the extension phase and the main study or Part 2 (≥50 exposure days in the extension phase) or until the approval of the present application for damoctocog alfa pegol. Any subject experiencing a bleed was to receive damoctocog alfa pegol at a dose up to 60 IU/kg, according to the type, location, and severity of the bleed. Any subject undergoing minor surgery was to receive damoctocog alfa pegol before surgery and an additional infusion 24 to 48 hours after the preoperative infusion as indicated. Further infusion was considered according to the subject’s condition.

Of the 61 subjects completing the main study or Part 2 of Study 15912, fifty-nine (59) subjects (32 subjects aged <6 years and 27 subjects aged ≥6 and <12 years) were enrolled in the extension phase. All of the 59 subjects enrolled in the extension phase received at least 1 dose of damoctocog alfa pegol and

⁶⁾ ABR = (total number of spontaneous and traumatic bleeding episodes × 365.25 × 24 × 60)/duration of treatment with damoctocog alfa pegol (minutes)
Data on bleeding events were collected in Study 21824, regardless of treatment status, while no data on bleeding events not requiring treatment were collected in Study 15912.

⁷⁾ This subject reported epistaxis at the same frequency before the start of the study and underwent surgery during the study period, which resulted in a decreased number of postoperative bleeding episodes.

were included in the SAF. Subjects in the SAF who had treatment or bleeding data in the electronic patient diary (all the subjects in the SAF) were included in the intent-to-treat (ITT) population.

In the SAF, the number of damoctocog alfa pegol exposure days per subject (mean $\pm$ SD [range]) in the extension phase was 373.7 $\pm$ 139.3 [42, 612] days (333.7 $\pm$ 149.7 [42, 597] days in subjects aged <6 years, 421.2 $\pm$ 110.6 [210, 612] days in subjects aged $\geq$ 6 and <12 years). In addition, 58 subjects (98.3%) achieved $\geq$ 100 exposure days.

Adverse events were reported in 94.9% (56 of 59) of subjects (96.9% [31 of 32] of subjects aged <6 years, 92.6% [25 of 27] of subjects aged $\geq$ 6 and <12 years) in the extension phase. Adverse events reported in $\geq$ 5 subjects in any group are shown in Table 5.

Table 5. Adverse events reported in $\geq$ 5 subjects (Study 15912 [extension phase], SAF)

	Subjects aged $\geq$ 6 and <12 years (N = 27)	Subjects aged <6 years (N = 32)	All subjects (N = 59)
Event term	n (%)	n (%)	n (%)
Headache	13 (48.1)	3 (9.4)	16 (27.1)
Nasopharyngitis	10 (37.0)	9 (28.1)	19 (32.2)
Oropharyngeal pain	9 (33.3)	5 (15.6)	14 (23.7)
Epistaxis	8 (29.6)	8 (25.0)	16 (27.1)
Pain in extremity	8 (29.6)	6 (18.8)	14 (23.7)
Pyrexia	7 (25.9)	17 (53.1)	24 (40.7)
Arthralgia	7 (25.9)	4 (12.5)	11 (18.6)
Abdominal pain	7 (25.9)	2 (6.3)	9 (15.3)
Cough	6 (22.2)	10 (31.3)	16 (27.1)
Vomiting	6 (22.2)	6 (18.8)	12 (20.3)
Rhinitis	6 (22.2)	3 (9.4)	9 (15.3)
Influenza	5 (18.5)	5 (15.6)	10 (16.9)
Joint injury	5 (18.5)	5 (15.6)	10 (16.9)
Fall	5 (18.5)	2 (6.3)	7 (11.9)
Ligament sprain	5 (18.5)	2 (6.3)	7 (11.9)
Head injury	4 (14.8)	9 (28.1)	13 (22.0)
Diarrhoea	4 (14.8)	3 (9.4)	7 (11.9)
Nausea	4 (14.8)	3 (9.4)	7 (11.9)
Pain	4 (14.8)	1 (3.1)	5 (8.5)
Contusion	3 (11.1)	7 (21.9)	10 (16.9)
Gastroenteritis	3 (11.1)	5 (15.6)	8 (13.6)
Upper respiratory tract infection	3 (11.1)	6 (18.8)	9 (15.3)
Post-traumatic pain	3 (11.1)	4 (12.5)	7 (11.9)
Tendonitis	3 (11.1)	3 (9.4)	6 (10.2)
Limb injury	2 (7.4)	8 (25.0)	10 (16.9)
Tonsillitis	2 (7.4)	5 (15.6)	7 (11.9)
Ear infection	2 (7.4)	3 (9.4)	5 (8.5)
Pharyngitis	2 (7.4)	3 (9.4)	5 (8.5)
Pharyngitis streptococcal	2 (7.4)	3 (9.4)	5 (8.5)
Subcutaneous haematoma	2 (7.4)	3 (9.4)	5 (8.5)
Haematoma	1 (3.7)	5 (15.6)	6 (10.2)
Gingival bleeding	1 (3.7)	4 (12.5)	5 (8.5)
Haemarthrosis	1 (3.7)	4 (12.5)	5 (8.5)
Sinusitis	0	5 (15.6)	5 (8.5)

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A total of 5 study drug-related adverse events were reported in 4 subjects (6.8%), which included 1 event of anti factor VIII antibody positive and 1 event of arthralgia in 1 subject ($\geq$ 6 and <12 years); 2 events of anti factor VIII antibody positive in 2 subjects (1 event in 1 subject aged $\geq$ 6 and <12 years, 1 event in 1 subject aged <6 years), and 1 event of muscle spasms in 1 subject (aged <6 years). In the subjects

with anti factor VIII antibody positive, low-titer factor VIII inhibitors were suspected in the first measurement but not detected in the second measurement, and no anti-damoctocog alfa pegol antibodies were detected by enzyme-linked immunosorbent assay (ELISA). All of these events resolved.

A total of 40 serious adverse events were reported in 20 subjects (33.9%) (19 events in 7 subjects aged ≥ 6 and < 12 years, 21 events in 13 subjects aged < 6 years). The events reported in subjects aged ≥ 6 and < 12 years included 2 events of anti factor VIII antibody positive in 2 subjects; 2 events of abdominal pain in 2 subjects; 2 events of gastritis in 1 subject; 2 events of Crohn's disease in 1 subject; and 1 event each of device-related sepsis, device occlusion, viral infection, synoviorrhesis, somnolence, haemarthrosis, physical assault, headache, otitis media, pneumonia, and diplopia in 1 subject each. The events reported in subjects aged < 6 years included 4 events of haemarthrosis in 4 subjects; 3 events of head injury in 3 subjects; 2 events of syncope in 1 subject; and 1 event each of gastroenteritis, pharyngeal haemorrhage, cardiomyopathy, inguinal hernia, central venous catheter removal, appendicitis, cryptorchism, skin laceration, abdominal wall haematoma, tonsillar inflammation, concussion, and fibula fracture in 1 subject each. The 2 events of anti factor VIII antibody positive in the 2 subjects aged ≥ 6 and < 12 years were assessed as related to damoctocog alfa pegol. An adverse event leading to discontinuation of damoctocog alfa pegol occurred in 1 subject aged < 6 years (cardiomyopathy), which was assessed as unrelated to damoctocog alfa pegol. Except for this cardiomyopathy event, all of these events resolved. No deaths were reported during the study.

As for efficacy, the median ABR⁶⁾ for bleeds requiring treatment [range] in the extension phase was 1.64 [0.0, 17.5] bleeds/year (1.54 [0.0, 17.5] bleeds/year in subjects aged < 6 years, 1.89 [0.0, 8.3] bleeds/year in subjects aged ≥ 6 and < 12 years). The hemostatic efficacy of damoctocog alfa pegol for bleeds requiring treatment was rated as "excellent" or "good" in 87.4% (583 of 667) of the bleeding events (92.9% [300 of 323 events] in subjects aged < 6 years, 82.3% [283 of 344 events] in subjects aged ≥ 6 and < 12 years) by subjects or their parents (caregivers) according to the criteria shown in Table 4. During the extension phase, 14 subjects underwent 17 minor surgeries. The hemostatic efficacy of damoctocog alfa pegol rated by the surgeon or investigator (sub-investigator) at minor surgery according to the criteria shown in Table 6 was "excellent" or "good" in all cases, except for 1 event (tooth extraction) rated as "moderate."

Table 6. Perioperative rating scale^{a)}

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

a) Intra-operative response to treatment was assessed by the surgeon or the investigator (sub-investigator), and post-operative response to treatment was assessed by the surgeon.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical data package and review strategy

The applicant's explanation about the clinical data package for the present application:

The present application is intended to extend the indication of damoctocog alfa pegol from patients aged ≥ 12 years to those aged ≥ 7 years and to add a dosage regimen for patients aged ≥ 7 and < 12 years to the

dosage and administration. For the present application, a foreign phase III study (Study 21824 [main study]) was newly planned in order to further evaluate the potential risks of hypersensitivity reactions and loss of efficacy associated with anti-PEG antibodies (AESIs) within the first 4 exposure days with damoctocog alfa pegol in previously treated patients aged ≥ 7 and < 12 years with hemophilia A. This study was designed similarly to Study 15912 (main study) on the assumption that the safety and efficacy of damoctocog alfa pegol would be evaluated based on pooled data from subjects enrolled in this study and 25 subjects aged ≥ 7 and < 12 years at the time of enrollment in the foreign phase III study (Study 15912 [main study]), which was submitted as the evaluation data for the initial approval. The pooled analysis plan was developed before the results of Study 21824 (main study) became available. Table 7 shows major differences between the study plans; however, because of limited impact of these differences on the safety and efficacy evaluations, the applicant considered it possible to evaluate the safety and efficacy of damoctocog alfa pegol based on pooled data from the two studies [see Sections 7.R.2 and 7.R.3].

Table 7. Major differences between the plans of Study 21824 (main study) and Study 15912 (main study)

	Study 21824 (main study)	Study 15912 (main study)
Country	Argentina, Brazil, Canada, Italy, Norway, Turkey, the US	Argentina, Austria, Belgium, Bulgaria, Canada, the UK, Israel, Italy, Lithuania, the Netherlands, Poland, Romania, the US
Inclusion criteria	Male children aged ≥ 7 and <12 years	Male children aged <12 years ^{a)}
Exclusion criteria	Patient with a FVIII inhibitor titer ≥ 0.6 BU/mL at screening. Patient receiving any FVIII product within 2-3 weeks before testing and not within 48 hours ^{b)} before screening sample collection.	Patient with a FVIII inhibitor titer >0.6 BU/mL at screening. Patient receiving any FVIII product within 2-3 weeks before testing and not within 72 hours before screening sample collection.
	Patient scheduled to undergo major surgery during the treatment period. ^{c)}	None
	Patient subcutaneously receiving a commercially available FVIII replacement product (emicizumab) in the past 6 months. ^{d)}	None
	Patient previously participating in a clinical trial of damoctocog alfa pegol.	None
Treatment groups	40 IU/kg (allowed to be increased up to 60 IU/kg), ^{e)} twice weekly	25-60 IU/kg twice weekly 45-60 IU/kg every 5 days 60 IU/kg every 7 days
Definition of AESI	Loss of efficacy is defined as an abnormally low FVIII activity level in the absence of FVIII inhibitors (i.e., FVIII activity unable to detect or lower than 15 IU/dL with high-titer anti-PEG antibodies [higher than 1:16] after administration, or insufficient <i>in vivo</i> recovery to maintain FVIII activity associated with anti-PEG antibodies, despite modification of the dose and/or dosing interval to maintain adequate prophylaxis of bleeding. However, if adequate prophylaxis of bleeding is achieved with increased doses and/or reduced dosing intervals, low recovery and/or FVIII activity after administration are not considered loss of efficacy).	Loss of efficacy ^{f)} is defined as clinically suspected loss of efficacy as evident by unexpected bleeding, or lack of or inadequate response to damoctocog alfa pegol treatment for bleeding, in the opinion of the investigator (or sub-investigator) (for suspected subjects, the FVIII activity levels before and after administration of damoctocog alfa pegol are confirmed and recorded by central testing).

a) The pooled analysis was performed using data from 25 subjects aged ≥ 7 and <12 years.

b) The washout period was reduced because treatment practices at the time when Study 15912 (main study) had been conducted approximately 10 years earlier were different from the ones at the time of Study 21824 (main study). Specifically, prophylactic treatment was the standard of care treatment instead of on-demand treatment, and some subjects were receiving alternate-day treatment.

c) Although this criterion was not used in Study 15912 (main study), there were actually no subjects aged ≥ 7 and <12 years who underwent surgery. Therefore, this criterion was specified to align the subject characteristics.

d) Because emicizumab was not approved at the time of Study 15912 (main study), this criterion was specified to avoid differences in subject characteristics.

e) In Study 15912 (main study), most subjects were treated twice weekly or every 5 days at the discretion of the physician. In Study 21824, therefore, twice-weekly dosing was evaluated in the main study and not only twice-weekly dosing but also every-5-day dosing was allowed in the ongoing extension phase.

f) No subjects aged ≥ 7 and <12 years met the definition of loss of efficacy.

Although the Japanese population is not included in the clinical data package, the applicant considers that the safety and efficacy data of damoctocog alfa pegol in Study 15912 (main study and extension phase) and Study 21824 (main study) can be extrapolated to the Japanese population for the following reasons:

- (1) Intrinsic and extrinsic ethnic factors are unlikely to significantly affect the efficacy and safety of damoctocog alfa pegol because of the similarities between Japan and other countries in the epidemiological characteristics of patients with hemophilia A, diagnostic procedures, severity classification, pathology, treatment policy, response of plasma FVIII to the dose of FVIII products, etc.
- (2) The change in plasma FVIII activity and pharmacokinetic parameters were similar between the Japanese and non-Japanese populations aged ≥ 18 years⁸⁾ in Study 13024.³⁾ Drug metabolizing

⁸⁾ Study 13024 was planned to include patients aged ≥ 12 and ≤ 65 years with severe hemophilia A, but enrolled no Japanese patients aged <18 years.

enzymes showing genetic polymorphism are not involved in the elimination of a protein product, damoctocog alfa pegol, and its pharmacokinetics is unlikely to be affected by ethnic differences. Based on these findings, no differences in the pharmacokinetics are likely to be observed between Japanese and non-Japanese patients aged ≥ 7 and < 12 years.

- (3) At the initial approval of damoctocog alfa pegol, based on the results of Study 13024 and Study 15912 (main study) as well as the reasons (1) and (2) above, it was suggested that the efficacy of damoctocog alfa pegol observed in the entire study population of patients with hemophilia A could be expected also in the Japanese population, along with a favorable safety profile in patients aged ≥ 12 years.

PMDA's view:

As with the conclusion reached for the initial approval, intrinsic and extrinsic ethnic factors are unlikely to significantly affect the efficacy and safety of damoctocog alfa pegol because of the similarities between Japan and other countries in the epidemiological characteristics of patients with FVIII deficiency including those with hemophilia A, pathological conditions of bleeding tendency, treatment concept of FVIII replacement to control and prevent bleeding episodes, etc. in patients aged ≥ 7 and < 12 years. A national survey reported that a total of 5,956 patients had hemophilia A in Japan, including 682 patients aged ≥ 6 and < 15 years (Project entrusted by Ministry of Health, Labour and Welfare, Nationwide Survey of Patients with Coagulation Disorders 2024). The number of patients aged ≥ 7 and < 12 years with hemophilia A who will be eligible for use of damoctocog alfa pegol is extremely limited in Japan. In light of the circumstances above and the applicant's explanation, the efficacy and safety of damoctocog alfa pegol in Japanese patients aged ≥ 7 and < 12 years could be evaluated based on the results of Study 15912 (main study and extension phase) and Study 21824 (main study), although no Japanese subjects were included in these studies.

In this review, the efficacy and safety of damoctocog alfa pegol in patients aged ≥ 7 and < 12 years are evaluated based on the results of pooled analysis of the main studies of Studies 15912 and 21824. In addition, the results of Study 15912 (extension phase) are also reviewed to evaluate the long-term safety and efficacy of damoctocog alfa pegol.

7.R.2 Efficacy

The applicant explained the efficacy of damoctocog alfa pegol, as described in Sections 7.R.2.1 to 7.R.2.4 below.

7.R.2.1 Efficacy of prophylactic treatment

For efficacy evaluation, a pooled analysis was performed using data from subjects aged ≥ 7 and < 12 years in Study 15912 (main study) and from Study 21824 (main study). The efficacy analysis set included subjects aged ≥ 7 and < 12 years with severe hemophilia A who received at least 1 dose of damoctocog alfa pegol, had ≥ 3 -month electronic patient diary data, and did not develop FVIII inhibitors. Damoctocog alfa pegol was administered to 60 subjects (35 in Study 21824 [main study] and 25 in Study 15912 [main study]). Of these, 57 subjects (32 in Study 21824 [main study] and 25 in Study 15912 [main study]) were included in the pooled efficacy analysis set, and the remaining 3 subjects who did not complete Study 21824 (main study) were excluded from the analysis. The primary efficacy endpoint

was ABR⁹⁾ for bleeds requiring treatment, which was evaluated separately in 2 subject populations classified by the dosing interval of damoctocog alfa pegol (twice-weekly treatment group¹⁰⁾ and overall treatment group¹¹⁾). The twice-weekly treatment group included 32 of the 32 subjects in Study 21824 (main study) and 10 of the 25 subjects in Study 15912 (main study).

In the twice-weekly treatment group and the overall treatment group, the number of damoctocog alfa pegol exposure days per subject (mean $\pm$ SD [range]) was 53.8 ± 4.0 [35, 62] days and 53.8 ± 3.8 [35, 63] days, respectively, and 41 (97.6%) and 56 (98.2%) subjects, respectively, achieved ≥ 50 exposure days.

ABRs for bleeds requiring treatment are shown in Table 8.

Table 8. ABRs⁹⁾ for bleeds requiring treatment (pooled analysis, efficacy analysis set)

		Twice-weekly treatment (N = 42)	Overall treatment (N = 57)	
All bleeding episodes	No. of subjects with bleeds requiring treatment		12	25
	No. of bleeds requiring treatment (episodes)		36 ^{a)}	84 ^{a)}
	ABR (bleeds/year)	Mean ± SD	1.7 ± 3.0	2.5 ± 3.4
		Median [range]	0.0 [0, 10]	0.0 [0, 11]
		Estimate [95% CI] ^{b)}	1.96 [1.01, 3.82]	2.30 [1.58, 3.36]
Spontaneous bleeding	No. of subjects with bleeds requiring treatment		8	17
	No. of bleeds requiring treatment (episodes)		20 ^{a)}	42 ^{a)}
	ABR (bleeds/year)	Mean ± SD	0.9 ± 2.0	1.3 ± 2.1
		Median [range]	0.0 [0, 8]	0.0 [0, 8]
Traumatic bleeding	No. of subjects with bleeds requiring treatment		8	15
	No. of bleeds requiring treatment (episodes)		15 ^{a)}	4 ^{a)}
	ABR (bleeds/year)	Mean ± SD	0.7 ± 1.9	1.2 ± 2.3
		Median [range]	0.0 [0, 10]	0.0 [0, 10]
Intra-articular bleeding	No. of subjects with bleeds requiring treatment		8	15
	No. of bleeds requiring treatment (episodes)		20	43
	ABR (bleeds/year)	Mean ± SD	0.9 ± 2.1	1.3 ± 2.3
		Median [range]	0.0 [0, 8]	0.0 [0, 8]

a) There was no information available to identify the type of bleeding (either spontaneous or traumatic) for 1 dose in 1 subject in Study 21824. Therefore, the total number of spontaneous and traumatic bleeding episodes does not match the total number of all bleeding episodes.

b) Estimate based on a negative binomial regression model with study as a covariate and evaluation period as an offset variable

7.R.2.2 Efficacy of on-demand treatment

Table 9 shows the number of damoctocog alfa pegol infusions for bleeding episodes and the rating of hemostatic efficacy in the pooled efficacy analysis set. In both the twice-weekly treatment group and overall treatment group, $\geq 80\%$ of the bleeding episodes were controlled with a single infusion of damoctocog alfa pegol, with a small number of bleeds requiring ≥ 2 infusions of damoctocog alfa pegol. The hemostatic efficacy of damoctocog alfa pegol for bleeding events was rated according to the criteria shown in Table 4, with hemostatic efficacy rated as “excellent” or “good” for most bleeding episodes.

⁹⁾ ABR (bleeds/year) = (total number of spontaneous, traumatic, and intraarticular bleeding episodes, or total bleeding episodes [total number of spontaneous and traumatic bleeding episodes] $\times$ 365.25 $\times$ 24 $\times$ 60)/duration of treatment with damoctocog alfa pegol (minutes)

¹⁰⁾ Twice-weekly treatment group: Subjects who received prophylactic treatment with damoctocog alfa pegol twice weekly for at least 3 months during each study period without changing the dosing interval. This group was defined as the primary pooled efficacy analysis set because twice-weekly prophylactic treatment was provided in both studies.

¹¹⁾ Overall treatment group: All subjects who received damoctocog alfa pegol, regardless of the dosing interval (including the twice-weekly treatment group).

All subjects including those receiving damoctocog alfa pegol at an increased dosing interval were evaluated because subjects achieving a therapeutic effect with treatment at an increased dosing interval were expected to respond to treatment even at a twice-weekly dosing interval.

The dosing interval was increased only in Study 15912 (main study).

Table 9. Number of damoctocog alfa pegol infusions for bleeding episodes and rating of hemostatic efficacy (pooled analysis, efficacy analysis set)

		Twice-weekly treatment (N = 42)	Overall treatment (N = 57)
No. of bleeds requiring treatment (episodes)		36	84
No. of damoctocog alfa pegol infusions required (infusions, % ^{a)})	1	30 (83.3)	68 (81.0)
	2	5 (13.9)	10 (11.9)
	≥3	1 (2.8)	6 (7.1)
Hemostatic efficacy (episodes, % ^{a)})	Excellent	10 (27.8)	28 (33.3)
	Good	20 (55.6)	39 (46.4)
	Moderate	5 (13.9)	14 (16.7)
	Poor	1 (2.8)	3 (3.6)

a) Percentage to the number of bleeds requiring treatment

7.R.2.3 Efficacy of perioperative management

No subject with perioperative management was included in the pooled efficacy analysis set. In Study 15912 (extension phase), of the 27 subjects aged ≥ 6 and < 12 years,¹²⁾ 6 subjects underwent 8 minor surgeries, and the hemostatic efficacy of damoctocog alfa pegol rated at the minor surgery according to the criteria shown in Table 6 was “excellent” or “good” in all cases, except for 1 event (tooth extraction) rated as “moderate.” No major surgery was performed during the study period including the extension phase.

7.R.2.4 Long-term efficacy

The median ABR [range] in the 27 subjects aged ≥ 6 and < 12 years¹²⁾ in Study 15912 (extension phase) was 1.89 [0.0, 8.3] bleeds/year, which was lower than that in the main study (2.92 [0.0, 11.0] bleeds/year). The hemostatic efficacy for bleeds requiring treatment (344 events) rated as “excellent” or “good” was 82.3% (283 of 344) of the bleeding events [see Section 7.2].

In conclusion, although no statistical hypothesis testing was planned, the pooled analysis has demonstrated the efficacy of damoctocog alfa pegol in prophylactic treatment for prevention of bleeding and on-demand treatment and control of bleeding episodes in previously treated patients aged ≥ 7 and < 12 years with severe hemophilia A. Study 15912 (extension phase) also has demonstrated the efficacy of damoctocog alfa pegol in controlling bleeding tendency when administered as prophylactic treatment and in achieving hemostasis when administered as on-demand treatment and perioperative management, indicating that the long-term efficacy of damoctocog alfa pegol is favorable on the whole.

PMDA’s view:

Based on the results of Study 13024 (global study) as the pivotal study as well as Study 15912 (main study) conducted in children aged < 12 years, the efficacy of damoctocog alfa pegol in controlling bleeding tendency when administered as prophylactic treatment and in achieving hemostasis when administered as on-demand treatment and perioperative management was evaluated for the initial approval. The study results indicated that its efficacy in children aged < 12 years was similar to that observed in children aged ≥ 12 years. The pooled analysis has demonstrated that the efficacy of damoctocog alfa pegol in patients aged ≥ 7 years and < 12 years is consistent with that confirmed for the initial approval. Study 15912 (extension phase) has also confirmed the efficacy of damoctocog alfa

¹²⁾ Consisting of 3 subjects aged 6 years and 24 subjects aged ≥ 7 and < 12 years.

pegol in controlling bleeding tendency when administered as prophylactic treatment and in achieving hemostasis when administered as on-demand treatment and perioperative management. The efficacy in patients aged ≥ 7 and < 12 years is expected to be similar to that confirmed for the initial approval.

7.R.3 Safety

The applicant explained the safety of damoctocog alfa pegol, as described in Sections 7.R.3.1 to 7.R.3.3 below.

7.R.3.1 Safety in the pooled analysis

The applicant's explanation about the safety assessed in the pooled analysis using the data from subjects aged ≥ 7 and < 12 years in Study 15912 (main study) and the data from Study 21824 (main study) [see Section 7.R.1]:

All the 60 subjects aged ≥ 7 and < 12 years receiving at least 1 dose of damoctocog alfa pegol (35 in Study 21824 [main study] and 25 in Study 15912 [main study]) were included in the SAF. Of these, 1 subject in Study 21824 (main study) discontinued treatment within the first 4 exposure days for a reason other than occurrence of AESI. The primary endpoint was the proportion of subjects with AESI occurring within the first 4 exposure days and leading discontinuation or interruption of damoctocog alfa pegol. Subjects with any suspected AESI underwent testing for ADAs and inhibitors. Loss of efficacy was determined based on the FVIII activity levels before and after administration of damoctocog alfa pegol analyzed centrally.

Table 10 shows the incidence of adverse events between the first dose and 7 days after the last dose of damoctocog alfa pegol in each study in the SAF for the pooled analysis of the main studies of Studies 15912 and 21824.

Table 10. Summary of adverse events (pooled analysis, SAF [N = 60])

		n (%)
Any adverse event		38 (63.6)
Severity	Mild	25 (41.7)
	Moderate	11 (18.3)
	Severe	2 (3.3)
Study drug-related adverse events		4 (6.7)
Severity	Mild	1 (1.7)
	Moderate	3 (5.0)
Adverse events leading to treatment discontinuation		0
Serious adverse events		3 (5.0)
Serious study drug-related adverse events		0
Death		0
AESI		1 (1.7)

Most of the reported adverse events were mild or moderate in severity. A total of 4 severe adverse events were reported in 2 subjects (1 event each of haemorrhage intracranial, subarachnoid haemorrhage, and device connection issue in 1 subject; 1 event of gastroenteritis in 1 subject). A total of 8 serious adverse events were reported in 3 subjects (1 event each of photophobia, nausea, haemorrhage intracranial, headache, subarachnoid haemorrhage, and device connection issue in 1 subject; 1 event of gastroenteritis in 1 subject; and 1 event of abdominal pain in 1 subject). All these events resolved and were assessed as unrelated to damoctocog alfa pegol. No adverse events leading to treatment discontinuation or deaths were reported.

No subject discontinued the study due to adverse events; however, 1 subject (aged 8 years) in Study 21824 (main study) experienced AESI (loss of efficacy) on Day 2 of exposure. This subject was considered to have loss of efficacy because of the development of high-titer (1:64) anti-PEG IgM antibodies with low *in vivo* recovery (FVIII activity of 4.5% after the third dose). Damoctocog alfa pegol treatment was interrupted, and the FVIII product used before this study was administered until the disappearance of the anti-PEG antibodies. The disappearance of the anti-PEG antibodies was confirmed with a sample collected approximately 1 month after the interruption of damoctocog alfa pegol treatment, and the subject restarted damoctocog alfa pegol 2 months after the interruption. After restarting dosing, the subject showed normal *in vivo* recovery with no immune response and continued receiving damoctocog alfa pegol in Study 21824 (extension phase).

Table 11 shows adverse events reported in $\geq 5\%$ of subjects in the SAF. A total of 6 adverse events were assessed as related to damoctocog alfa pegol in 4 subjects (3 events of infusion site pain in 1 subject, 1 event of drug ineffective, 1 event of injection site pruritus, and 1 event of epistaxis in 1 subject). All the events resolved, except for infusion site pain.

Table 11. Adverse events reported in $\geq 5\%$ of subjects (pooled analysis, SAF [N = 60])

Event	n (%)
Headache	9 (15.0)
Pyrexia	5 (8.3)
Cough	5 (8.3)
Viral infection	4 (6.7)
Pain in extremity	4 (6.7)
Oropharyngeal pain	4 (6.7)
Abdominal pain upper	3 (5.0)
Vomiting	3 (5.0)
Gastroenteritis	3 (5.0)
Influenza	3 (5.0)
Nasopharyngitis	3 (5.0)
Sinusitis	3 (5.0)
Tonsillitis	3 (5.0)
Arthralgia	3 (5.0)
Epistaxis	3 (5.0)

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AESIs occurring within the first 4 exposure days as the primary endpoint for the pooled analysis of the main studies of Studies 15912 and 21824 as well as the development of inhibitors and the development of ADAs were investigated, as described below.

(1) Hypersensitivity reactions and loss of efficacy associated with anti-PEG antibodies

For the pooled analysis of the main studies of Studies 15912 and 21824, AESIs occurring within the first 4 exposure days were evaluated based on the following points:

- In Study 15912 (main study) and Study 13024 which was conducted in previously treated patients (aged ≥ 12 and ≤ 65 years) with severe hemophilia A, hypersensitivity reactions occurred, and 4 subjects who were positive for anti-PEG antibodies (including 3 subjects also experiencing loss of efficacy) had hypersensitivity reactions within the first 4 exposure days.
- Of 4 subjects experiencing loss of efficacy only, 3 subjects had an inadequate increase in FVIII activity (including levels below the quantitation limit) by the fourth exposure day. The remaining 1

subject had a low FVIII activity after administration, which precluded calculation of the *in vivo* recovery on the fifth exposure day. However, their parents or guardian provided a report suggesting loss of efficacy by the second to fourth exposure days, and the investigator also reported an adverse event of “drug specific antibody present” by the third exposure day, albeit no antibody measurement results submitted.

- In some subjects, anti-PEG antibodies were detected from the fifth exposure day onward. However, since anti-PEG antibodies were measured at protocol-specified visits, the onset of AESI did not necessarily coincide with the measurement of anti-PEG antibodies.
- Post-marketing safety data for damoctocog alfa pegol were also generally consistent with the characteristics of AESIs observed in Study 15912 (main study) and Study 13024 in both of which loss of efficacy and hypersensitivity reactions occurred within the first 4 exposure days with damoctocog alfa pegol.
- In clinical and post-marketing surveillance studies of a PEGylated recombinant FVIII product, turoctocog alfa pegol (genetical recombination), in previously untreated patients with hemophilia A, a decreased FVIII *in vivo* recovery rate in the absence of inhibitors associated with anti-PEG immunoglobulin G (IgG) antibodies was observed within the first 5 exposure days (*Blood Adv.* 2023;7:620-9; *Haemophilia.* 2023;29:1475-82).
- No class switch to IgG was reported for detected anti-PEG antibodies.

Of the subjects in the SAF, 1 discontinued treatment within the first 4 exposure days for a reason other than occurrence of AESI. Of the remaining 59 subjects, 1 reported loss of efficacy leading to temporary interruption of damoctocog alfa pegol treatment [see Section 7.R.3.1]. No subjects experienced hypersensitivity reactions to damoctocog alfa pegol.

Due to the expected low incidence of AESI, Study 21824 (main study) was planned on the assumption that study data would be pooled with data from subjects aged ≥ 7 and < 12 years in Study 15912, and the incidence of AESI within the first 4 exposure days in subjects aged ≥ 7 and < 12 years was estimated by the Bayesian method¹³⁾ based on the pooled data from both studies. For the above 59 subjects (1 event of AESI in 1 of the 34 subjects from Study 21824 [main study] and 0 events of AESI in 0 of the 25 subjects from Study 15912 [main study]), Bayesian analysis showed that the mean and median [two-sided 90% confidence interval (CI)] of the posterior distribution of the incidence of AESI in subjects aged ≥ 7 and < 12 years were 2.1% and 1.59% [0.18%, 5.76%], respectively, and the posterior probability that the incidence of AESI was $< 5\%$ was 92.2%.

(2) Development of inhibitors, and development of anti-damoctocog alfa pegol antibodies and anti-PEG antibodies

In the SAF for the pooled analysis of the main studies of Studies 15912 and 21824, no subjects developed an inhibitor against FVIII after administration of damoctocog alfa pegol.

¹³⁾ The posterior distribution was estimated assuming that the prior distribution of the incidence of AESI was beta distribution (1/4, 1/4) and the development of AESI followed a beta-binomial distribution. As a summary of the posterior distribution, the mean and median [two-sided 90% CI] and the posterior probability of the incidence of AESI being $< 5\%$ were calculated.

The development of anti-damoctocog alfa pegol antibodies, anti-PEG antibodies, and anti-PEG IgM antibodies was determined by ELISA¹⁴⁾ in all subjects in the main studies of Studies 15912 and 21824. At baseline, anti-damoctocog alfa pegol antibodies were detected in 1 subject, both anti-damoctocog alfa pegol antibodies and anti-PEG antibodies were detected in 2 subjects, and only anti-PEG IgM antibodies were detected in 2 subjects. In all the subjects, antibodies were low-titers (1:1 to 1:4) and not detected at the final measurement. Four subjects developed de novo anti-PEG IgM antibodies during treatment and tested negative at the final measurement, except for 2 subjects who discontinued the study for reasons other than adverse events and were lost to follow-up. These antibodies were detected before the third or fourth dose. All the subjects presented low-titer antibodies, except for 1 subject who developed high-titer (1:64) anti-PEG IgM antibodies. In 2 of these subjects, mildly decreased *in vivo* recovery (lowest value of 0.8 kg/dL) was observed, but both cases were not associated with adverse events or loss of efficacy of the study drug. The 1 subject exhibiting high titers was the 8-year-old subject who had AESI (loss of efficacy) on the second exposure day, as described above. This subject also transiently tested positive for anti-damoctocog alfa pegol antibodies but was negative for all antibodies at the final visit. All the anti-PEG antibodies were of the IgM isotype produced transiently, and no class switching to IgG was observed.

7.R.3.2 Long-term safety

The applicant's explanation about the long-term safety of damoctocog alfa pegol:

Table 12 shows a safety summary in subjects aged ≥ 6 and < 12 years in Study 15912 (extension phase). Most of the reported adverse events were mild or moderate in severity. A total of 3 adverse events related to damoctocog alfa pegol were reported in 2 subjects (1 event of anti factor VIII antibody positive and 1 event of arthralgia in 1 subject and 1 event of anti factor VIII antibody positive in 1 subject). A total of 2 serious adverse events related to damoctocog alfa pegol were reported in 2 subjects (2 events of anti factor VIII antibody positive in 2 subjects) [see Section 7.2]. No deaths or adverse events related to loss of efficacy or hypersensitivity were reported. No inhibitors against FVIII or anti-PEG antibodies were detected. No evidence of PEG accumulation was detected.

Table 12. Summary of adverse events (Study 15912 [extension phase], subjects aged ≥ 6 and < 12 years, SAF)

		n (%) N = 27
Any adverse event		25 (92.6)
Severity	Mild	5 (18.5)
	Moderate	19 (70.4)
	Severe	1 (3.7)
Study drug-related adverse events		2 (7.4)
Severity	Mild	1 (3.7)
	Moderate	1 (3.7)
Adverse events leading to treatment discontinuation		0
Serious adverse events		7 (25.9)
Serious study drug-related adverse events		2 (7.4)
Death		0
AESI		0

¹⁴⁾ Antibodies that bind to an arbitrary portion of damoctocog alfa pegol (anti-damoctocog alfa pegol antibodies) and antibodies that bind to the PEG moiety (Cys-Linker PEG) (anti-PEG antibodies) were determined by a measurement method that has the highest specificity to IgG but is targeted for antibodies of all isotypes. IgM antibodies that specifically bind to the PEG moiety (anti-PEG IgM antibodies) were determined as needed.

Of the 27 subjects aged ≥ 6 and < 12 years, 3 subjects were 6 years, all of whom reached 7 years during the study. These 3 subjects reported 49, 22, and 17 adverse events, all of which were assessed as unrelated to damoctocog alfa pegol. One subject experienced 4 serious adverse events (1 event each of viral infection, otitis media, pneumonia, and physical assault), which resolved. Therefore, exclusion of these 3 subjects from the data of the 27 subjects aged ≥ 6 and < 12 years is unlikely to substantially affect the interpretation of the results. Thus, the applicant considers it possible to extrapolate the data on the safety of damoctocog alfa pegol from subjects aged ≥ 6 and < 12 years in Study 15912 (extension phase) to subjects aged ≥ 7 and < 12 years for its long-term safety.

Although not included in the clinical data package for the present application, the preliminary results (data cut-off on August 31, 2024) of the ongoing Study 21824 (extension phase) have revealed no particular safety concerns.

7.R.3.3 Post-marketing safety information

The applicant's explanation about the post-marketing safety information for damoctocog alfa pegol: The most recent Periodic Benefit Risk Evaluation Report (PBRER) for damoctocog alfa pegol (August 29, 2023 to August 28, 2024) has provided no new information that may modify the overall benefit-risk assessment for damoctocog alfa pegol.

Information on the off-label use in 20 patients aged < 12 years, who were all non-Japanese, was obtained by August 28, 2024. Of the 20 patients, 10 were reported to be ≥ 7 and < 12 years of age, and no safety concerns were identified in any of them.

As described in Sections 7.R.3.1 to 7.R.3.3 above, the risks associated with the use of damoctocog alfa pegol in patients aged ≥ 7 and < 12 years are considered to be generally within the range of the safety information accrued so far, with no new safety concerns identified.

PMDA's view:

The submitted clinical study results and post-marketing safety information have identified no safety concerns specific to children aged ≥ 7 and < 12 years; therefore, the safety of damoctocog alfa pegol is tolerable. The development of inhibitors against FVIII and the development of anti-PEG antibodies have been defined as the important identified risks in the risk management plan for damoctocog alfa pegol. When new information becomes available, it should be communicated to healthcare professionals appropriately and promptly.

7.R.4 Dosage and administration

7.R.4.1 Age of the intended population

At the initial approval, the applicant excluded children aged <12 years from the intended population for damoctocog alfa pegol for the following reasons¹⁵⁾:

- Because loss of efficacy suspected to be associated with anti-PEG antibodies was observed more frequently in patients aged <6 years than in patients aged ≥6 years, a favorable benefit-risk profile of damoctocog alfa pegol cannot be established.
- Although the safety profile in patients aged ≥6 and <12 years was shown to be similar to that in patients aged ≥12 years, the age at which the risk of an immune response to PEG is sufficiently reduced or eliminated is unclear.

The applicant's justification for proposing the minimum age of 7 years for use of damoctocog alfa pegol in the present application:

Table 13 shows the occurrence of loss of efficacy and hypersensitivity reactions and the proportion of subjects with an event suspected to be associated with anti-PEG antibodies in Study 15912 (main study and Part 2) by age group. Of 44 subjects aged <6 years, 11 subjects experienced loss of efficacy. Of these, 1 subject developed neutralizing antibodies to damoctocog alfa pegol, and the remaining 10 subjects did not develop neutralizing antibodies to damoctocog alfa pegol, but loss of efficacy was suspected to be associated with anti-PEG antibodies. Hypersensitivity reactions occurred in 3 subjects, all of which were suspected to be associated with anti-PEG antibodies. Of the 29 subjects aged ≥6 and <12 years, in contrast, no subjects experienced loss of efficacy, and hypersensitivity reaction occurred in 1 subject (aged 6 years), which was not associated with anti-PEG antibodies. Some subjects tested positive for anti-PEG antibodies before dosing of damoctocog alfa pegol but exhibited no clinical symptoms. It was, therefore, difficult to predict the occurrence of loss of efficacy and hypersensitivity reactions based on the anti-PEG antibody status before dosing.¹⁶⁾

Table 13. Occurrence of loss of efficacy and hypersensitivity reactions leading to study discontinuation by age group (safety analysis set)

	Study 15912 (main study and Part 2)		Studies 15912 and 21824 (main study)	Study 13024 (main study and extension phase)
	<6 years (N = 44)	≥6 and <12 years (N = 29)	≥7 and <12 years (N = 60)	≥12 years (N = 134)
Subjects with loss of efficacy	11 subjects ^{a)}	0 subjects	1 subject	0 subjects
Of whom, those with loss of efficacy suspected to be associated with anti-PEG antibodies	10/11 subjects ^{b)}	-	1/1 subject	-
Subjects with hypersensitivity reactions	3 subjects	1 subject	0 subjects	2 subjects
Of whom, those with hypersensitivity reactions suspected to be associated with anti-PEG antibodies	3/3 subjects	0/1 subjects	-	1/2 subjects

a) Of these subjects, 3 had hypersensitivity reactions as well.

b) Including 1 subject in whom no anti-PEG antibody was detected but neutralizing antibodies to damoctocog alfa pegol were detected.

¹⁵⁾ See Section 7.R.3 of the "Review Report for Jivi for IV Injection 250, Jivi for IV Injection 500, Jivi for IV Injection 1000, Jivi for IV Injection 2000, Jivi for IV Injection 3000 dated August 2, 2018."

¹⁶⁾ See Section 7.R.3.2 of the "Review Report for Jivi for IV Injection 250, Jivi for IV Injection 500, Jivi for IV Injection 1000, Jivi for IV Injection 2000, Jivi for IV Injection 3000 dated August 2, 2018."

In Study 15912 (main study), none of subjects aged ≥ 7 and < 12 years reported loss of efficacy or hypersensitivity reactions. In subjects with loss of efficacy and hypersensitivity reactions suspected to be associated with the development of anti-PEG antibodies after dosing of damoctocog alfa pegol, only IgM was identified as the anti-PEG antibody type, and no class switching to IgG was observed. These findings suggest that only the innate immune response that develops during the fetal period was induced, but adaptive immunity was not triggered. In addition, given that maturation of B-1 cells that produce anti-PEG IgM antibodies occurs at approximately 5 to 6 years of age (*Eur J Immunol.* 2017;47:327-44), the immune response is also thought to change at 5 to 6 years of age. With individual differences in the maturation rate also taken into consideration, Study 21824 was designed to enroll patients aged at least 7 years. The pooled analysis using the data from subjects aged ≥ 7 and < 12 years in Study 15912 (main study) and the data from Study 21824 (main study) shows that damoctocog alfa pegol is effective not only in patients aged ≥ 12 years but also in previously treated patients aged ≥ 7 and < 12 years with severe hemophilia A, demonstrating a favorable benefit- risk balance of damoctocog alfa pegol, with no new safety issues identified.

PMDA's view:

Loss of efficacy suspected to be associated with anti-PEG antibodies was observed in many subjects aged < 6 years in Study 15912 (main study and Part 2), and loss of efficacy suspected to be associated with anti-PEG antibodies was observed in 1 subject aged 8 years on the second exposure day with damoctocog alfa pegol in the additionally conducted Study 21824 (main study). Given these results, it is still unclear at what age the level of anti-PEG antibody formation is inferred to be as low as that in individuals aged ≥ 12 years. However, it is possible to extend the indication of damoctocog alfa pegol to include patients aged at least 7 years, taking into account the following 3 reasons: (1) It is understandable to some extent that the applicant enrolled patients aged ≥ 7 years in Study 21824 because none of the subjects aged ≥ 7 and < 12 years experienced loss of efficacy or hypersensitivity reactions suspected to be associated with anti-PEG antibodies in Study 15912 (main study); (2) treatment with damoctocog alfa pegol was resumed, after disappearance of anti-PEG antibodies, even in the subject aged 8 years experiencing loss of efficacy suspected to be associated with the anti-PEG antibodies in Study 21824 (main study); and (3) no new safety issues were identified in the pooled analysis using the data from subjects aged ≥ 7 and < 12 years in Study 15912 (main study) and the data from Study 21824 (main study). However, because of the limited information from patients aged ≥ 7 and < 12 years, safety information in clinical practice should be collected through routine pharmacovigilance activities, and if any new finding becomes available, it should be communicated to healthcare professionals appropriately and promptly [see Section 7.R.5].

7.R.4.2 Dosage regimen for prophylactic treatment

The proposed dosage and administration was “for children aged ≥ 7 and < 12 years, the usual regimen for routine prophylaxis is 40 to 60 IU/kg body weight twice weekly.”

The applicant's explanation about the background and reason for selecting the dosage regimen:

For the doses for clinical studies in subjects aged < 12 years, in Study 15912 (main study), damoctocog alfa pegol for prophylactic treatment was administered at 25 to 60 IU/kg twice weekly, 45 to 60 IU/kg every 5 days, or 60 IU/kg every 7 days, and the dosage was adjusted by the investigator according to

the clinical needs of each subject based on activity level, previous bleeding episodes, etc. In Study 21824 (main study), damoctocog alfa pegol was administered at 40 IU/kg based on the mean dose per dose (41.5 IU/kg) for prophylactic treatment in subjects aged ≥ 6 and < 12 years and the maximum dose (60 IU/kg) in Study 15912 (main study), and the dose was allowed to be increased up to 60 IU/kg at any time at the investigator's discretion.

In Study 15912 (main study and extension phase), damoctocog alfa pegol was allowed to be administered twice weekly, every 5 days, or once weekly. However, considering that most subjects were treated twice weekly or every 5 days at the investigator's discretion, in Study 21824, twice-weekly dosing was evaluated in the main study and every-5-day dosing was also permitted in the ongoing extension phase.

As per the pooled analysis of the main studies of Studies 15912 and 21824, the mean $\pm$ SD [range] of the dose per prophylactic treatment in the twice-weekly treated group (N = 42) was 48.87 ± 12.99 [22.2, 69.1] IU/kg. In Study 15912 (main study), some subjects started treatment with damoctocog alfa pegol at a low dose of 25 IU/kg and had their dose increased to 35 to 40 IU/kg within the first 2 months of treatment.

Based on the above results and consideration that high-dose damoctocog alfa pegol should be frequently administered to children for prophylactic treatment due to the generally shorter half-life of FVIII in children than in adults (Hemostatic Treatment Guidelines for Hemophilia Patients without Inhibitors: 2013 revised edition [Japanese Society on Thrombosis and Hemostasis Guidelines] and World Federation of Hemophilia Guidelines for the Management of Hemophilia, 3rd edition [WFH Guidelines]), the dosage regimen of 40 to 60 IU/kg body weight twice weekly was proposed for dosage and administration. The necessity of every-5-day dosing will be separately examined based on the results to be obtained in the extension phase of Study 21824.

The appropriate starting dose of damoctocog alfa pegol was examined, as described below.

Analyses were performed to provide the background and reason for selecting the appropriate starting dose. In Study 13024 (subjects aged ≥ 12 and ≤ 65 years) submitted for the initial approval, the *in vivo* recovery rate from the first dose to Week 36 ranged from 2.54 to 2.75 kg/dL, showing almost no fluctuations. In Study 21824 (main study) (subjects aged ≥ 7 and < 12 years), however, the *in vivo* recovery rates were 1.53 to 1.76 kg/dL within the first 4 exposure days and 2.06 kg/dL at Month 6. Thus, the *in vivo* recovery rates in subjects aged ≥ 7 and < 12 years tended to be slightly low at an early stage of dosing and were lower than those in subjects aged ≥ 12 years from the first dose through Month 6 (≥ 50 exposure days).

In Study 21824 (main study), the target starting dose was 50 to 60 IU/kg in 18 subjects (56.3%) and < 50 IU/kg in 14 subjects (43.8%). Of the 14 subjects with a target starting dose of < 50 IU/kg, 10 subjects had their dose increased by > 5 IU/kg mainly within the first 2 months and 9 subjects achieved a dose of ≥ 55 IU/kg. In Study 21824 (main study), all of 4 subjects with a starting dose of 60 IU/kg remained on the dose of 60 IU/kg twice weekly until the end of the main study. After Month 6 or > 50 exposure days

when treatment with damoctocog alfa pegol was considered to have stabilized, 11 of 28 subjects with a starting dose of <60 IU/kg had their dose increased. Consequently, the actual dose (median) increased from 48.64 IU/kg at baseline to 56.94 IU/kg, which was not markedly different from the dose (59.77 IU/kg) in subjects with a starting dose of 60 IU/kg.

In Study 15912 (main study), only data from subjects treated with different dosing intervals were available and FVIII activity was not measured from the first dose through Month 3. It was therefore difficult to use the data for the evaluation of the starting dose of 60 IU/kg.

As described above, a certain number of patients had a slightly decreased *in vivo* recovery rate at an early stage of dosing. It is necessary to ensure adequate FVIII activity levels in pediatric patients and to avoid a potential risk of increased bleeding frequency due to a slight decrease in FVIII activity. To this end, the applicant determined to include a precaution for the starting dose, stating that “if the product is administered to children aged ≥ 7 and <12 years as prophylactic treatment, the starting dose of 60 IU/kg body weight is desirable” in the Precautions Concerning Dosage and Administration section. It will be determined individually how long the starting dose of 60 IU/kg should be continued.

PMDA’s view:

Based on the review results on the efficacy and safety of damoctocog alfa pegol in the pooled analysis of the main studies of Studies 15912 and 21824 (Sections 7.R.2 and 7.R.3), which are the pivotal data for the present application, and given the dosage regimens and actual administration status in these 2 studies, damoctocog alfa pegol may be administered at a dose of 40 to 60 IU/kg twice weekly. In addition, as in patients aged ≥ 12 years, the dosage regimen for prophylactic treatment in patients aged ≥ 7 and <12 should be selected, according to the patient’s conditions such as the latest bleeding status.

The applicant’s explanation that many subjects with a starting dose of <60 IU/kg had their dose increased in Study 21824 (main study) is understandable to a certain extent. However, in light of the following points, it is not considered necessary to provide a uniform precaution for the recommended starting dose of damoctocog alfa pegol, regardless of the patient’s condition. This issue will be further reviewed taking into account of comments from the Expert Discussion.

- In Study 21824 (main study), damoctocog alfa pegol was administered at a dose of 40 IU/kg twice weekly. The dose was allowed to be increased up to 60 IU/kg in each subject based on activity level, previous treatment, etc. at the investigator’s discretion at any time during the study period. Thus, patients were treated appropriately with an increased dose in consideration of their condition, etc.
- In routine clinical settings, an appropriate starting dose can be selected based on the patient’s activity level and previous treatment at the investigator’s discretion and the bleeding can be controlled appropriately by increasing the dose as necessary, even though no precaution is advised for the recommended starting dose proposed by the applicant.
- The dose of 60 IU/kg is included in the range of the proposed dosage and administration (40 to 60 IU/kg).

It is desirable to examine the necessity of every-5-day dosing in the future, in view of the results of Study 21824 (extension phase) and the needs of healthcare professionals.

7.R.4.3 Dosage regimen for on-demand treatment

The applicant's explanation:

The dosage regimen for on-demand treatment at the initial approval was "For patients aged ≥ 12 years, the usual dose is 10 to 30 IU/kg body weight. This may be adjusted according to the patient's condition." There is no dosage regimen for on-demand treatment, including perioperative management, established specifically for patients aged ≥ 7 and < 12 years.

In the main studies of Studies 15912 and 21824, the doses to be used for on-demand treatment were determined for each subject according to the site and severity of bleeding, the subject's previous treatment, and the investigator's discretion. On-demand treatment was provided for 9 of 32 subjects (21 events) in Study 21824 (main study) and 18 of 25 subjects aged ≥ 7 and < 12 years (63 events) in Study 15912 (main study), including 5 of 10 subjects treated twice weekly (15 events). The median dose of damoctocog alfa pegol per on-demand treatment was 55.35 IU/kg in Study 21824 (main study), 47.67 IU/kg in Study 15912 (main study), and 25.64 IU/kg for twice-weekly dosing. In both Studies 21824 and 15912, bleeding occurred most frequently in joints, and $\geq 90\%$ of bleeding episodes were controlled with 1 or 2 infusions of damoctocog alfa pegol. The hemostatic efficacy of damoctocog alfa pegol was rated as "excellent" or "good" for most of the bleeding episodes [see Section 7.R.2].

The doses of damoctocog alfa pegol used for on-demand treatment in clinical studies tended to be the same as those used for prophylactic treatment. This result would not necessarily indicate the doses required for bleeding control because of presumed practical reasons including the following: Damoctocog alfa pegol was administered mainly by subjects' parents (caregivers) in the main studies of Studies 15912 and 21824 and they easily opted for doses commonly used for prophylactic treatment; and hemostasis is often considered to be achieved even with scheduled prophylactic treatment.

The mean *in vivo* recovery rate in children aged ≥ 7 and < 12 years without ADAs (twice-weekly dosing) confirmed in the main studies of Studies 15912 and 21824 was approximately 1.9 kg/dL. Most of the bleeding episodes confirmed in children aged ≥ 7 and < 12 years in the main studies of Studies 15912 and 21824 were mild or moderate in severity, which usually require a FVIII activity level of 20% to 60% for controlling bleeding. Based on these findings, the dose of damoctocog alfa pegol essentially required for on-demand treatment is thought to be within the range of 10 to 30 IU/kg in most cases. A patient with a low *in vivo* recovery rate or a severe bleeding episode can be addressed by "adjusting the dose according to the patient's condition."

For on-demand treatment including perioperative management, the Japanese and foreign guidelines (Japanese Society on Thrombosis and Hemostasis Guidelines and WFH Guidelines) recommended that the amount of a FVIII concentrate to be infused should be calculated based on the target blood FVIII activity level according to the type, severity, and site of bleeding and adjusted according to the condition of individual patients (e.g., circulating plasma volume, complications, CL).

In conclusion, the dose of 10 to 30 IU/kg for on-demand treatment in patients aged ≥ 7 and < 12 years, which is the same as that in patients aged ≥ 12 years is appropriate, and the dose should be appropriately adjusted according to the patient's condition.

PMDA considers that the applicant's explanation is acceptable, and that the dosage regimen for patients aged ≥ 7 and < 12 years as proposed is appropriate.

7.R.5 Post-marketing investigations

The applicant's explanation:

Post-marketing surveillance for the present application may not be conducted immediately after approval is obtained, and safety information on damoctocog alfa pegol should be collected through routine pharmacovigilance activities based on the following considerations:

- The pooled analysis of data from patients aged ≥ 7 and < 12 years did not show any safety profile different from that in patients aged ≥ 12 years. Therefore, there seems to be no newly identified safety issue for the present application.
- The pooled analysis showed a markedly lower incidence of hypersensitivity reactions and loss of efficacy (AESIs) associated with anti-PEG antibodies in patients aged ≥ 7 and < 12 years (1.7%) than in patients aged < 6 years (22.7%) in Study 15912 (main study and Part 2).
- Since the initial approval of damoctocog alfa pegol, healthcare professionals in medical institutions have been informed about the measures to be taken against suspected anti-PEG antibody formation (including reports of adverse events). The applicant considers it possible to collect safety information on suspected anti-PEG antibody formation and take safety measures against it by newly preparing materials for healthcare professionals and continuing proactive provision of information on proper use and spontaneous reporting once the present application has been approved.
- The applicant considers it difficult to conduct meaningful post-marketing surveillance, etc. because an estimated number of patients aged ≥ 7 and < 12 years who will use damoctocog alfa pegol after the approval of the present application is approximately 2.7 patients/5 years (0 to 1 new patients per year).

PMDA's view:

More information on anti-PEG antibody formation in patients aged ≥ 7 and < 12 years treated with damoctocog alfa pegol is needed for the following reasons: (i) The small number of subjects was evaluated in clinical studies for the present application; and (ii) there is insufficient rationale to support the comparable risks between patients aged ≥ 7 and < 12 years and patients aged ≥ 12 years because of the reported loss of efficacy associated with anti-PEG antibody formation in 1 subject aged 8 years in Study 21824 (main study). To this end, the applicant should collect further information in clinical practice, desirably through post-marketing surveillance, etc., once the present application for use in patients aged ≥ 7 and < 12 years has been approved. However, the applicant considers that the estimated number of patients using damoctocog alfa pegol after approval of the present application may preclude the conduct of post-marketing surveillance, and that the applicant will therefore prepare materials for healthcare professionals and strengthen routine pharmacovigilance activities, thereby collecting safety information on anti-PEG antibody formation in patients receiving damoctocog alfa pegol. The applicant's intention is understandable to some extent.

Post-marketing pharmacovigilance activities and risk minimization activities will be further reviewed, taking also account of comments raised in the Expert Discussion.

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

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

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

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

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

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

On the basis of the data submitted, PMDA has concluded that damoctocog alfa pegol has efficacy in controlling bleeding tendency in patients with blood coagulation factor VIII deficiency when administered at the proposed dosage and administration, and that damoctocog alfa pegol has acceptable safety in view of its benefits.

PMDA has concluded that damoctocog alfa pegol may be approved if damoctocog alfa pegol is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

August 6, 2025

Product Submitted for Approval

Brand Name	Jivi for IV Injection 500 Jivi for IV Injection 1000 Jivi for IV Injection 2000 Jivi for IV Injection 3000
Non-proprietary Name	Damoctocog Alfa Pegol (Genetical Recombination)
Applicant	Bayer Yakuhin, Ltd.
Date of Application	October 30, 2024

List of Abbreviations

See Appendix.

1. Content of the Review

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

1.1 Efficacy and dosage and administration

At the Expert Discussion, the expert advisors supported the PMDA's conclusions presented in Sections "7.R.2 Efficacy" and "7.R.4 Dosage and administration" in the Review Report (1), and made the following comments:

- Considering that the twice-weekly doses for prophylactic treatment for patients aged <12 years (40-60 IU/kg) hardly overlap with those for patients aged ≥12 years (30-40 IU/kg), the applicant should provide healthcare professionals with information about how patients who start treatment with damoctocog alfa pegol at 7 to 11 years of age should switch to the dosage regimen for patients aged ≥12 years when they become 12 years of age.
- Given multiple possible factors contributing to the shorter half-life of FVIII in children, the appropriate dose should be determined according to the patient's condition. Therefore, the use of a high starting dose should not be uniformly recommended for children aged ≥7 and <12 years.

The applicant explained that the dosage for patients starting prophylactic treatment with damoctocog alfa pegol at the age of 7 to 11 years would be switched to the dosage regimen for patients aged ≥12 years while gradually adjusting the dosing interval and dose according to the patient's condition. Further,

the applicant will provide information to healthcare professionals, for example, by preparing materials, as needed, according to use status in clinical practice.

PMDA accepted the applicant's explanation. In addition, PMDA requested the applicant to delete the uniform precaution for the recommended starting dose of 60 IU/kg of damoctocog alfa pegol, regardless of the patient's condition [see Section 7.R.4.2] from the Precautions Concerning Dosage and Administration. The applicant accepted it.

1.2 Safety and post-marketing investigations

At the Expert Discussion, the expert advisors supported the PMDA's conclusions presented in Sections "7.R.3 Safety" and "7.R.5 Post-marketing investigations" in the Review Report (1), and made the following comments:

- After the approval of the present application, the applicant is requested to further inform healthcare professionals of cases in which the presence of FVIII inhibitors and anti-PEG antibodies is suspected and to ensure that they avoid dose increases without careful consideration in patients with any event suggesting loss of efficacy, take appropriate actions for the patients, such as switching of products and identification of causes, and report safety information.
- In the event of loss of efficacy or decreased *in vivo* recovery, information on the presence or absence of FVIII inhibitors and anti-PEG antibodies would be useful in selecting another product. In addition, since the measures to ensure the safety of damoctocog alfa pegol should continue to be evaluated based on the anti-PEG antibody status, it is meaningful to further inform healthcare professionals of the necessity of anti-PEG antibody measurement after the approval of the present application, thereby collecting information.
- Loss of efficacy suspected to be associated with anti-PEG antibodies may be newly reported also in patients aged ≥ 7 and < 12 years. Therefore, a system to measure anti-PEG antibodies should be maintained for several years even after the approval of the present application.
- Since the development of an inhibitor against modified FVIII products may occur in the post-marketing setting even if not observed in clinical studies, the applicant should collect post-marketing safety information on the development of FVIII inhibitors also in patients receiving damoctocog alfa pegol.

PMDA thus asked the applicant to take the following actions, and the applicant agreed to respond appropriately:

- Inform healthcare professionals of cases in which the presence of FVIII inhibitors and anti-PEG antibodies is suspected, by using measures including the package insert, risk management plan, and materials.
- Maintain a system to measure anti-PEG antibodies in the event of loss of efficacy suggesting anti-PEG antibody formation for a certain period of time even after the approval of the present application.

1.3 Risk management plan (draft)

In view of the discussions presented in Section "7.R.5 Post-marketing investigations" in the Review Report (1) and the comments from the expert advisors at the Expert Discussion presented in Section 1.2 herein, PMDA has concluded that the risk management plan (draft) for damoctocog alfa pegol is

acceptable, provided that the applicant will collect safety information through routine pharmacovigilance activities by preparing and providing materials for healthcare professionals concerning the anti-PEG antibody formation associated with treatment with damoctocog alfa pegol as additional risk minimization activities, as shown in Table 15, in addition to the current activities.

Table 14. Safety specifications in the risk management plan (draft)

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

(No change in the present application)

Table 15. Summary of additional pharmacovigilance activities and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Use-results survey (patients aged ≥ 12 years)	• Organize and disseminate informative materials to healthcare professionals (“Measurement of plasma coagulation factor VIII activity after administration of Jivi for IV Injection” <u>and “Development of anti-PEG antibodies after administration of Jivi for IV Injection”</u>)

(Underline denotes addition. Completed activities are not included in the table.)

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indication and dosage and administration as shown below, with the following approval condition. The re-examination period for the present application is the remainder of the re-examination period for the initial approval of the product (until September 20, 2026).

Indication

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

(No change)

Dosage and Administration

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

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

For patients aged ≥ 12 years, the usual regimen for routine prophylaxis is 30 to 40 IU/kg body weight twice weekly. The regimen may be adjusted to 45 to 60 IU/kg body weight every 5 days or 60 IU/kg body weight once weekly, according to the patient’s condition. For children aged ≥ 7 and < 12 years, the usual regimen for routine prophylaxis is 40 to 60 IU/kg body weight twice weekly.

(Underline denotes additions. Strikethrough denotes deletions.)

Approval Condition

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

List of Abbreviations

ABR	Annualized bleeding rate
ADA	Anti-drug antibodies
AESI	Adverse event of special interest
AUC	Area under the plasma concentration-time curve
CL	Clearance
C _{max}	Maximum plasma concentration or activity
Concizumab	Concizumab (Genetical Recombination), Alhemo Subcutaneous Injection 15 mg, Alhemo Subcutaneous Injection 60 mg, Alhemo Subcutaneous Injection 150 mg, Alhemo Subcutaneous Injection 300 mg
CV	Coefficient of variation
Damoctocog alfa pegol	Damoctocog Alfa Pegol (Genetical Recombination)
ELISA	Enzyme-linked immunosorbent assay
Emicizumab	Emicizumab (Genetical Recombination), Hemlibra s.c. 30 mg, Hemlibra s.c. 60 mg, Hemlibra s.c. 90 mg, Hemlibra s.c. 105 mg, Hemlibra s.c. 150 mg
FVIII	Coagulation factor VIII
FIXa	Activated coagulation factor IX
FX	Coagulation factor X
IgG	Immunoglobulin G
IgM	Immunoglobulin M
Inhibitor	Neutralizing antibody against coagulation factor VIII
ITT	Intent-to-Treat
Japanese Society on Thrombosis and Hemostasis Guidelines	Hemostatic Treatment Guidelines for Hemophilia Patients without Inhibitors: 2013 revised edition. Edited by Committee for Preparation of the Hemostatic Treatment Guidelines for Hemophilia Patients without Inhibitors, the Japanese Society on Thrombosis and Hemostasis
Marstacimab	Marstacimab (Genetical Recombination), Hymoviz S.C. Injection 150 mg Pen
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
mITT	Modified Intent-to-Treat
MRT	Mean residence time
PBRER	Periodic Benefit Risk Evaluation Report
PEG	Polyethylene glycol
PMDA	Pharmaceuticals and Medical Devices Agency
SAF	Safety analysis set
t _{1/2}	Terminal half-life
TFPI	Tissue factor pathway inhibitor
V _{ss}	Volume of distribution at steady state
WFH Guidelines	World Federation of Hemophilia Guidelines for the Management of Hemophilia, 3rd edition