17 October 2024
EMA/CHMP/260738/2024
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Adynovi

Rurioctocog alfa pegol

Procedure no: EMEA/H/C/004195/P46/015

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	01 Apr 2024	01 Apr 2024
☐	CHMP Rapporteur Assessment Report	06 May 2024	06 May 2024
☐	CHMP members comments	21 May 2024	N/A
☐	Updated CHMP Rapporteur Assessment Report	23 May 2024	23 May 2024
☐	Request for Supplementary Information:	30 May 2024	30 May 2024
☐	Submission	17 Sep 2024	17 Sep 2024
☐	Re-start	18 Sep 2024	18 Sep 2024
☐	CHMP Rapporteur Assessment Report	02 Oct 2024	02 Oct 2024
☐	CHMP members comments	07 Oct 2024	N/A
☐	Updated CHMP Rapporteur Assessment Report	10 Oct 2024	N/A
☒	CHMP adoption of conclusions:	17 Oct 2024	17 Oct 2024

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Fulfilled: 55

1. Introduction

On 27 February 2024, the MAH submitted a completed paediatric study for Adynovi, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study 261601: ADYNOVATE drug use-results survey is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

Adynovate (marketed in the EU as Adynovi) contains rurioctocog alfa pegol, a pegylated recombinant human factor VIII (FVIII) with an extended half-life (EHL) due to the addition of a 20 kDa polyethylene glycol (PEG). It belongs to the pharmacotherapeutic group of blood coagulation FVIII (Anatomical Therapeutic Chemical code: B02BD02).

Conjugation with the hydrophilic PEG increases the molecular size of the FVIII concentrates and is expected to improve the pharmacokinetic (PK) profile, as well as extend the biological half-life (t1/2). ADYNOVATE (PEGylated, recombinant antihemophilic factor; Takeda), an EHL FVIII product, is a full-length form of ADVATE (recombinant antihemophilic factor; Takeda) covalently conjugated with a PEG moiety (ADYNOVATE (Antihemophilic Factor (Recombinant) PEGylated) 2023).

2.3. Clinical aspects

2.3.1. Introduction

ADYNOVATE has been confirmed to be safe and effective in clinical studies in patients with severe hemophilia A. However, because information on the safety and efficacy of ADYNOVATE in Japanese patients is limited and the use of ADYNOVATE is not limited to patients with severe hemophilia A, a drug use-results survey was conducted to investigate the safety and efficacy of ADYNOVATE in actual use in daily clinical practice.

In this submission, results from the completed ADYNOVATE drug use-results survey (Study 261601), which was conducted in Japan to investigate the safety and efficacy of ADYNOVATE in actual use in daily clinical practice, were summarised. This study included patients <18 years of age; thus, this submission is provided to comply with the requirements as stipulated in Article 46 of the European Union (EU) Pediatric Regulation (Regulation [EC] No 1901/2006, as amended).

The MAH submitted a final report for:

- Study 261601, ADYNOVATE drug use-results survey

ADYNOVATE drug use-results survey (Study 261601)

Description

The ADYNOVATE drug use-results survey (Study 261601) was conducted to understand the following items in the actual clinical use of ADYNOVATE:

- Unexpected adverse drug reactions (ADRs)

- Occurrence of ADRs in the actual clinical use of Adynovate
- Factors that could affect safety and efficacy
- Occurrence of FVIII inhibitor development in patients with hemophilia A
- Safety and efficacy for hemophilia A patients who received prophylaxis therapy and on-demand therapy

Hemophilia A patients who received ADYNOVATE in the real world clinical setting were eligible for enrollment in this survey. This included the following patients who were treated with ADYNOVATE at the contracting medical institutions.

- Previously treated patients who had 4 or more exposure days to other products (PTPs)
- Previously untreated or minimally treated patients who had 3 or less previous exposure days to other products (PUPs)

The observation period was 1 year after the beginning of Adynovate administration for PTPs and 2 years after the beginning of Adynovate administration for PUPs.

Methods

Study participants

Hemophilia A patients who received ADYNOVATE in the real world clinical setting were eligible for enrollment in this survey. This included PTPs and all PUPs who were treated with ADYNOVATE at the contracting medical institutions.

Treatments

Not applicable, as this was a drug use-results survey which aimed to investigate the safety and efficacy of Adynovate in actual use in daily clinical practice.

Objective(s), Outcomes/endpoints

The ADYNOVATE drug use-results survey (Study 261601) was conducted to understand the following items in the actual clinical use of ADYNOVATE:

- Unexpected adverse drug reactions (ADRs)
- Occurrence of ADRs in the actual clinical use of Adynovate
- Factors that could affect safety and efficacy
- Occurrence of FVIII inhibitor development in patients with hemophilia A
- Safety and efficacy for hemophilia A patients who received prophylaxis therapy and on-demand therapy

Assessor's comment

No formal definitions for objectives, outcomes, or endpoints were provided in the submission. According to the submitted cover letter, study documentation beyond the final study report, were only available in Japanese (including the study protocol and SAP) and therefore not provided. While this clearly is a limitation for the assessment of the provided data, this issue is not further pursued due to the exploratory character of the submitted survey.

Sample size

This survey was started by defining the target sample size as "PTPs, 120 patients; PUPs, no sample size predetermined," and the target sample size was changed to 165 (PTPs: 140 patients; PUPs: 25 patients) because of the expansion of the indication to children aged <12 years (partial change approval).

Sample size estimation rationale

Of the patients with hemophilia A in Japan, approximately 4,000 receive genetically recombinant human factor VIII products, of whom approximately 10% are expected to switch from the conventional products to ADYNOVATE in the period of 3 years after launching. However, launching and developments of other extended half-life genetically recombinant human factor VIII products for hemophilia A have been progressing. The number of patients who were actually going to receive ADYNOVATE was expected to fall below approximately one-half of the estimated number described above. Therefore, the target patient number was set to 140 PTPs as the number of collectable cases for ADYNOVATE safety examination. For PUPs, statistics show the birthrate of hemophilia A patients to be 1 out of 5,000 males and the number of annual male births to be 515,000, providing an estimated annual number of births with hemophilia A of 103. With a percentage of severe and moderate hemophilia A patients of 79.3% (2,137/2,696), it is estimated that there are 82 new patients receiving factor VIII annually. However, the target number of PUPs for 3 years after approval of supplemental New Drug Application for pediatrics is estimated at approximately 10% of the above–indicated number of patients treated with ADYNOVATE in view of the progress of clinical development or launch of similar products by competitors nowadays.

Randomisation and blinding (masking)

Not applicable.

Statistical Methods

Analysis sets

In this survey, two analysis sets, "safety analysis set" and "effectiveness analysis set," were established. The "safety analysis set" (patients included for safety evaluation) included the patients who did not meet the following criteria among those for whom registration was completed and CRFs were collected.

- Had not used ADYNOVATE or was unknown
- Had not made any visit after the initial prescription
- Presence or absence of adverse events unknown
- "Enrollment completion date" or "observation period completion date" was out of the contract period
- Not meeting enrollment criteria
- Registration form or previous separate volume not finalized

The "effectiveness analysis set" (patients included in efficacy evaluation) included the patients who did not meet the following criteria among those included in the safety evaluation.

- Off-label use
- Efficacy evaluation unclear

Patient composition was investigated using the following items:

Number of registered patients, number of patients whose CRFs are collected, number of patients included in the safety evaluation, number of patients included in the efficacy evaluation, number of withdrawal/discontinuation, reasons for and details of withdrawal/discontinuation, and others.

Items investigated related to safety were

- Occurrence of adverse events and adverse drug reactions/infections (type, severity and incidence, etc.)
- Factors that may affect safety (type and incidence of adverse drug reactions, etc. according to patient background)

Items investigated related to efficacy were

- Prophylaxis: ABR
- On-demand: hemostatic effectiveness, number of doses to treat a bleed

Physician-rated effectiveness ("poor," "fair," "good," or "excellent") using below evaluation criteria

Table 6.5.2.6-1 Criteria for the evaluation of treatment response

Excellent	Full relief of pain and cessation of objective signs of bleeding (e.g., swelling, tenderness, and decreased range of motion in the case of intraarticular hemorrhage) after a single infusion. No additional infusion is required for the control of bleeding. Administration of further infusions to maintain hemostasis would not affect this scoring.
Good	Definite pain relief and/or improvement in signs of bleeding after a single infusion. Possibly requires more than 1 infusion for complete resolution.
Fair	Probable and/or slight relief of pain and slight improvement in signs of bleeding after a single infusion. Required more than 1 infusion for complete resolution.
Poor	No improvement or condition worsens.

Assessor's comment

According to the provided study report, a statistical analysis plan was prepared and finalised before the CRFs for all patients were finalised (version 1 dating March 1, 2018, revision to version 2 dating June 8 2023). However, according to information received with the submission, the SAP was only available in Japanese and therefore not provided. The statistical methodology applied is therefore unclear.

Results

Recruitment/Participant flow/Number analysed

135 patients were registered from 66 medical institutions. Among the medical institutions from which patients were registered, the mean number of registered patients per medical institution was 2, the minimum number of registered patients was 1, and the maximum number of registered patients was 8. This survey had originally been conducted in patients who received ADYNOVATE for the first time, with a target sample size of 165 patients (140 PTPs and 25 PUPs). However, as the deadline for registration was set as "within 3 months after the start of administration of ADYNOVATE," the survey could not be conducted at medical institutions for which contract procedures were to be performed after the confirmation of administration because of the difficulty in meeting the registration deadline, and patients could not be registered immediately after the start of administration at contract medical institutions. For these reasons, the registration period ended with 135 registered patients.

Of the 135 registered patients, the CRFs were collected from all 135 patients. All patients whose CRFs were collected were included in the safety evaluation. Of the patients included in the safety evaluation, 131 patients were included in the efficacy evaluation, and 4 patients whose efficacy evaluation was unclear were excluded.

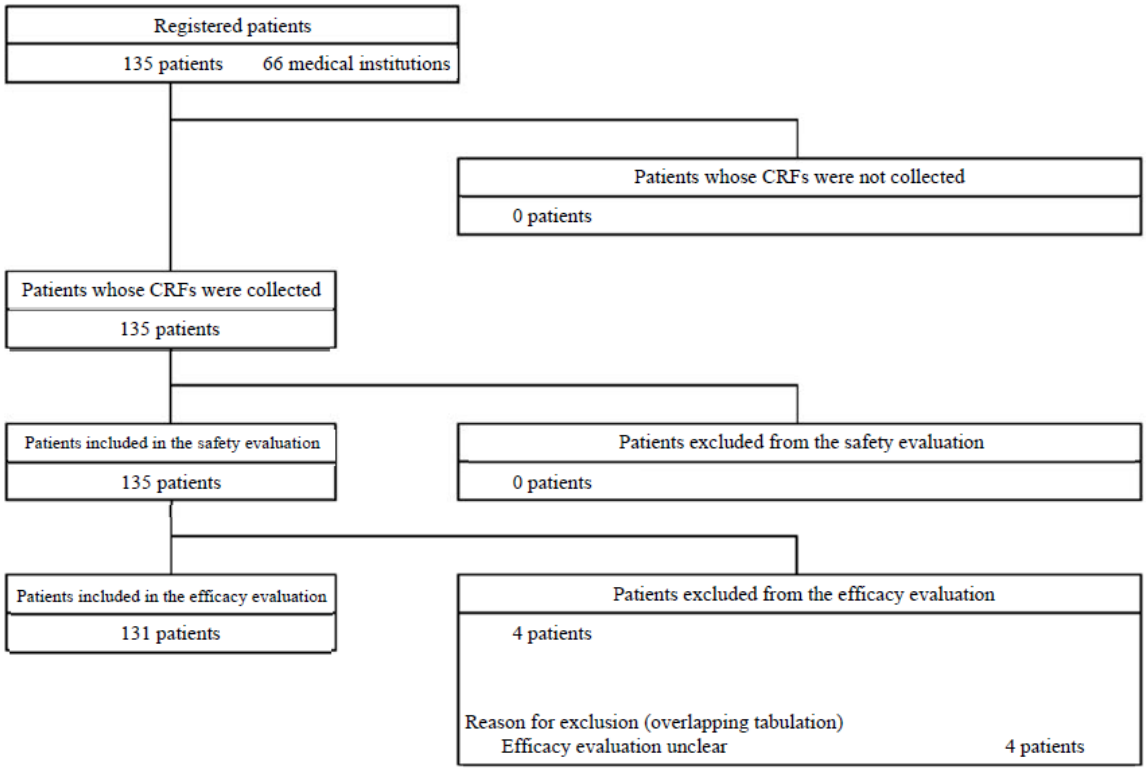

Figure 9.2-1 Patient composition

Details of treatment

The mean duration of long-term prophylaxis therapy was 353.0 days overall, with 343.0 days in PTPs and 510.7 days in PUPs. The mean dose per administration was 39.8 IU/kg overall, 39.4 IU/kg in PTPs, and 45.8 IU/kg in PUPs. The mean dosing frequency was 2.0 times per week overall, 2.0 times per week in PTPs, and 1.8 times per week in PUPs. The mean total number of doses was 96.2 overall, 93.4 in PTPs, and 140.7 in PUPs.

Baseline data

All patients had a confirmed diagnosis of congenital hemophilia A. Of 135 patients, 134 (99.26%) were male and 1 (0.74%) was female.

Most patients (80 [59.26%]) were 18-64 years old; 35 (25.3%) patients were aged <12 years, 5 (3.70%) patients were aged ≥12 and <18 years, 9 (6.67%) patients were aged ≥65 years and the age was unknown in 6 (4.44%) patients (date of birth and age cannot be provided).

By treatment history, among PTPs (N=123), most patients (77 [62.60%]) were 18-64 years old; 29 (23.58%) patients were aged <12 years, 4 (3.25%) patients were aged ≥12 and <18 years,

7 (5.69%) patients were aged ≥65 years and the age was unknown in 6 (4.88%) patients. Among PUPs (N=12), 6 (50.0%) patients were aged <12 years, 1 (8.33%) patient was aged ≥12 and <18 years, 3 (25.0%) patients were aged ≥18 and <65 years, and 2 (16.67%) patients were aged ≥65 years.

There were 33 (26.83%) patients in PTPs and 2 (16.67%) patients in PUPs with past history of bleeding episodes; the percentage of PTPs tended to be higher than that of PUPs. Hemophilic arthropathy was observed in 60 (48.78%) patients in PTPs and 3 (25.0%) patients in PUPs. There were 29 (23.58%) patients in PTPs and 4 (33.33%) patients in PUPs whose most recent annualized bleeding rate (ABR) was ≥0 and <1 times/year. The percentage of PUPs tended to be slightly higher than that of PTPs. Regarding other patient baseline characteristics, the number of patients in the PUP group was small and there was a limitation in interpretation; therefore, the difference could not be evaluated.

Table 10.1-1 Patient background (safety analysis set)

		Overall		PTPs		PUPs	
Patient background item	Levels	Number of patients	Percentage %	Number of patients	Percentage %	Number of patients	Percentage %
Number of patients included in safety evaluation		135	-	123	-	12	-
History of treatment with factor VIII products before administration of ADYNOVATE	4 or more days of administration (PTPs)	123	91.11	123	100.00	-	-
	3 or less days of administration (PUPs)	12	8.89	-	-	12	100.00
	Unknown*	0	0.00	-	-	-	-
Number of days of administration of factor VIII products before the administration of ADYNOVATE (cumulative)	0 to 3 days	12	8.89	0	0.00	12	100.00
	4 to 50 days	4	2.96	4	3.25	0	0.00
	51 to 150 days	3	2.22	3	2.44	0	0.00
	≥ 151 days	109	80.74	109	88.62	0	0.00
	Number of days of administration unknown	7	5.19	7	5.69	0	0.00
Gender	Male	134	99.26	123	100.00	11	91.67
	Female	1	0.74	0	0.00	1	8.33

Table 10.1-1 Patient background (safety analysis set) (continued)

		Overall		PTPs		PUPs	
Patient background item	Levels	Number of patients	Percentage %	Number of patients	Percentage %	Number of patients	Percentage %
Age (years)	< 12	35	25.93	29	23.58	6	50.00
	≥ 12 and < 18	5	3.70	4	3.25	1	8.33
	≥ 18 and < 65	80	59.26	77	62.60	3	25.00
	≥ 65	9	6.67	7	5.69	2	16.67
	Unknown (date of birth and age cannot be provided)	6	4.44	6	4.88	0	0.00
Medical care category	Inpatient	9	6.67	4	3.25	5	41.67
	Outpatient	126	93.33	119	96.75	7	58.33
Race	Asian	135	100.00	123	100.00	12	100.00
	White	0	0.00	0	0.00	0	0.00
	Black	0	0.00	0	0.00	0	0.00
	Other	0	0.00	0	0.00	0	0.00
Serious bleeding	No	110	81.48	98	79.67	12	100.00
	Yes	19	14.07	19	15.45	0	0.00
	Unknown	6	4.44	6	4.88	0	0.00
Surgical history	No	100	74.07	91	73.98	9	75.00
	Yes	29	21.48	27	21.95	2	16.67
	Unknown	6	4.44	5	4.07	1	8.33
Past history	No	96	71.11	86	69.92	10	83.33
	Yes	35	25.93	33	26.83	2	16.67
	Unknown	4	2.96	4	3.25	0	0.00
Breakdown of past history (overlapping tabulation)	Hepatitis C	26	19.26	25	20.33	1	8.33
	Hepatitis B	3	2.22	3	2.44	0	0.00
	Other	12	8.89	11	8.94	1	8.33
Complications	No	98	72.59	90	73.17	8	66.67
	Yes	35	25.93	32	26.02	3	25.00
	Unknown	2	1.48	1	0.81	1	8.33
Breakdown of complications (overlapping tabulation)	HIV infection	6	4.44	6	4.88	0	0.00
	Hypertension	15	11.11	13	10.57	2	16.67
	Hyperlipidemia	5	3.70	5	4.07	0	0.00
	Diabetes mellitus	6	4.44	6	4.88	0	0.00
	Gastric ulcer	2	1.48	2	1.63	0	0.00
	Chronic gastritis	5	3.70	5	4.07	0	0.00
	Anemia	2	1.48	1	0.81	1	8.33
	Epilepsy	2	1.48	2	1.63	0	0.00
	Depression	0	0.00	0	0.00	0	0.00
	Insomnia	8	5.93	8	6.50	0	0.00
	Other	15	11.11	15	12.20	0	0.00
Hemophilic arthropathy	No	69	51.11	61	49.59	8	66.67
	Yes	63	46.67	60	48.78	3	25.00
	Unknown	3	2.22	2	1.63	1	8.33
Target joint	No	110	81.48	100	81.30	10	83.33
	Yes	17	12.59	17	13.82	0	0.00
	Unknown	8	5.93	6	4.88	2	16.67
Hepatic impairment	No	126	93.33	114	92.68	12	100.00
	Yes	8	5.93	8	6.50	0	0.00
	Unknown	1	0.74	1	0.81	0	0.00

Table 10.1-1 Patient background (safety analysis set) (continued)

		Overall		PTPs		PUPs	
Patient background item	Levels	Number of patients	Percentage %	Number of patients	Percentage %	Number of patients	Percentage %
Breakdown of hepatic impairment (overlapping tabulation)	Hepatitis C	3	2.22	3	2.44	0	0.00
	Hepatitis B	1	0.74	1	0.81	0	0.00
	Cirrhosis	2	1.48	2	1.63	0	0.00
	Fatty liver	3	2.22	3	2.44	0	0.00
	Other	0	0.00	0	0.00	0	0.00
Renal impairment	No	132	97.78	120	97.56	12	100.00
	Yes	2	1.48	2	1.63	0	0.00
	Unknown	1	0.74	1	0.81	0	0.00
Breakdown of renal impairment (overlapping tabulation)	Diabetic nephropathy	1	0.74	1	0.81	0	0.00
	Renal calculus	0	0.00	0	0.00	0	0.00
	Other	1	0.74	1	0.81	0	0.00
Allergy	No	122	90.37	111	90.24	11	91.67
	Yes	8	5.93	7	5.69	1	8.33
	Unknown	5	3.70	5	4.07	0	0.00
Breakdown of allergy (overlapping tabulation)	Drug	3	2.22	3	2.44	0	0.00
	Food	3	2.22	2	1.63	1	8.33
	Pollen	2	1.48	2	1.63	0	0.00
	Other	1	0.74	1	0.81	0	0.00
Cause of hemophilia A	Congenital	135	100.00	123	100.00	12	100.00
	Acquired	0	0.00	0	0.00	0	0.00
Age at hemophilia A diagnosis (years)	< 1	41	30.37	38	30.89	3	25.00
	≥ 1 and < 12	31	22.96	28	22.76	3	25.00
	≥ 12 and < 18	4	2.96	3	2.44	1	8.33
	≥ 18 and < 65	7	5.19	4	3.25	3	25.00
	≥ 65	2	1.48	1	0.81	1	8.33
	Unknown	50	37.04	49	39.84	1	8.33
Most recent annualized bleeding rate (times/year)	≥ 0 and < 1	33	24.44	29	23.58	4	33.33
	≥ 1 and < 10	44	32.59	44	35.77	0	0.00
	≥ 10	14	10.37	14	11.38	0	0.00
	Unknown	44	32.59	36	29.27	8	66.67
Severity of hemophilia A (plasma residual factor VIII activity)	Severe (< 1%)	101	74.81	93	75.61	8	66.67
	Moderate (≥ 1% to < 5%)	18	13.33	16	13.01	2	16.67
	Mild (≥ 5%)	9	6.67	7	5.69	2	16.67
	Unknown (measured value unknown or not measured)	7	5.19	7	5.69	0	0.00
Status of administration of factor VIII products before the start of administration of ADYNOVATE (most recent)	Kovaltry	5	3.70	4	3.25	1	8.33
	Eloctate	1	0.74	1	0.81	0	0.00
	NovoEight	1	0.74	1	0.81	0	0.00
	Advate	105	77.78	102	82.93	3	25.00
	Kogenate FS	7	5.19	7	5.69	0	0.00
	Cross eight M/MC	5	3.70	5	4.07	0	0.00
	Confact F	2	1.48	1	0.81	1	8.33
	Other	2	1.48	2	1.63	0	0.00
	Not performed	7	5.19	0	0.00	7	58.33

Table 10.1-1 Patient background (safety analysis set) (continued)

		Overall		PTPs		PUPs	
Patient background item	Levels	Number of patients	Percentage %	Number of patients	Percentage %	Number of patients	Percentage %
Dosing regimen before the start of administration of ADYNOVATE (most recent)	Prophylaxis therapy	78	57.78	78	63.41	0	0.00
	On-demand replacement therapy	25	18.52	21	17.07	4	33.33
	Prophylaxis and on-demand replacement therapy	22	16.30	22	17.89	0	0.00
	Other	3	2.22	2	1.63	1	8.33
	Not performed	7	5.19	0	0.00	7	58.33
History of factor VIII inhibitor development	No	104	77.04	97	78.86	7	58.33
	Yes	7	5.19	7	5.69	0	0.00
	Unknown	24	17.78	19	15.45	5	41.67
Family history of hemophilia	No	56	41.48	52	42.28	4	33.33
	Yes	51	37.78	46	37.40	5	41.67
	Unknown	28	20.74	25	20.33	3	25.00
Family history of inhibitor development	No	90	66.67	85	69.11	5	41.67
	Yes	6	4.44	6	4.88	0	0.00
	Unknown	39	28.89	32	26.02	7	58.33
Pregnancy	No	1	100.00	0	0.00	1	100.00
	Yes	0	0.00	0	0.00	0	0.00
Concomitant drugs	No	94	69.63	89	72.36	5	41.67
	Yes	41	30.37	34	27.64	7	58.33
Concomitant therapies	No	134	99.26	122	99.19	12	100.00
	Yes	1	0.74	1	0.81	0	0.00

*Unknown: The CRFs were collected and tabulated as PTPs.
Percentage, %: Number of patients / Number of patients included in safety evaluation * 100

Assessor's comment

The overall study population was comprised of 135 HA patients. Regarding the paediatric study population, 35 (25.3%) patients were under 12 years of age, including 6 PUPs. 5 (3.7%) patients were ≥12 and <18 years of age, including 1 PUP. It is noted that the PTP definition applied (≥4 EDs) differs from the commonly used definition used in the EU (≥150 EDs). Baseline characteristics were not summarised according to age subgroups and no further comments on the demographics of the paediatric study population can therefore currently be made. A general request for additional analyses on paediatric subgroups is made.

Efficacy results

Of the patients included in the efficacy evaluation of prophylaxis therapy, 90.70% (117/129) of patients received long-term prophylaxis therapy. Of these, spontaneous bleeding occurred in 20.51% (24/117) of patients and breakthrough bleeding occurred in 27.35% (32/117) of patients. By treatment history, patients who received long-term prophylaxis therapy accounted for 92.44% (110/119 patients) in PTPs and 70.00% (7/10 patients) in PUPs. Among them, spontaneous bleeding occurred in 21.82% (24/110 patients) in PTPs, and breakthrough bleeding occurred in 28.18% (31/110 patients) in PTPs and 14.29% (1/7 patients) in PUPs.

The median annualized rate of spontaneous bleeding was 1.99 times/year (range, 1.00 to 3.59). By treatment history, the rate was 1.99 times/year (minimum, 0.9; maximum, 18.5) in PTPs.

The median annualized rate of breakthrough bleeding was 3.09 times/year (range, 1.54 to 5.01). By treatment history, the rate was 3.16 times/year (minimum, 0.9; maximum, 45.0) in PTPs and 2.91 times/year (minimum, 2.9; maximum, 2.9) in PUPs.

The ABR (spontaneous bleeding) in the long-term prophylaxis therapy is shown in Table 11.1.1-1, and the ABR (breakthrough bleeding, all bleeds occurring in patients on prophylaxis therapy) in the long-term prophylaxis therapy is shown in Table 11.1.1-2.

Table 11.1.1-1 Annualized bleeding rate (spontaneous bleeding) (long-term prophylaxis therapy) (effectiveness analysis set)

		Overall		PTPs		PUPs	
Prophylaxis therapy		Number of patients/ statistics	Percentage (%)	Number of patients/ statistics	Percentage (%)	Number of patients/ statistics	Percentage (%)
Number of patients included in efficacy evaluation		129*		119		10**	
Number of patients receiving long-term prophylaxis therapy		117	90.70	110	92.44	7	70.00
Number of patients with spontaneous bleeding during prophylaxis therapy		24	20.51	24	21.82	0	0.00
Annualized bleeding rate	Mean	3.08		3.08		-	
	Standard deviation	3.71		3.71		-	
	Minimum	0.9		0.9		-	
	First quartile	1.00		1.00		-	
	Median	1.99		1.99		-	
	Third quartile	3.59		3.59		-	
	Maximum	18.5		18.5			

Annualized bleeding rate = (number of spontaneous bleeding events during each treatment period/each treatment period) × 365.2425

*Two patients who received the prophylaxis therapy, "preventive treatment," were excluded from the patients included in the efficacy evaluation for prophylaxis therapy.

**In 2 PUPs, the details of "prophylaxis treatment" was "immune tolerance therapy" and "perioperative administration"; therefore, these patients were excluded from tabulation.

Table 11.1.1-2 Annualized bleeding rate (breakthrough bleeding) (long-term prophylaxis therapy) (effectiveness analysis set)

Prophylaxis therapy		Overall		PTPs		PUPs	
		Number of patients/ statistics	Percentage (%)	Number of patients/ statistics	Percentage (%)	Number of patients/ statistics	Percentage (%)
Number of patients included in efficacy evaluation		129*		119		10**	
Number of patients receiving long-term prophylaxis therapy		117	90.70	110	92.44	7	70.00
Number of patients with breakthrough bleeding during prophylaxis therapy		32	27.35	31	28.18	1	14.29
Annualized bleeding rate	Mean	5.14		5.21		2.91	
	Standard deviation	8.07		8.19		-	
	Minimum	0.9		0.9		2.9	
	First quartile	1.54		1.11		2.91	
	Median	3.09		3.16		2.91	
	Third quartile	5.01		5.10		2.91	
	Maximum	45.0		45.0		2.9	

Annualized bleeding rate = (number of breakthrough bleeding events during each treatment period/each treatment period) × 365.2425

*Two patients who received the prophylaxis therapy, "preventive treatment," were excluded from the patients included in the efficacy evaluation for prophylaxis therapy.

**In 2 PUPs, the details of "prophylaxis treatment" was "immune tolerance therapy" and "perioperative administration"; therefore, these patients were excluded from tabulation.

Hemostatic effectiveness of treatment of breakthrough bleeding during prophylaxis therapy

Of 122 patients who received prophylaxis therapy, 139 breakthrough bleeding events occurred in 35 patients (28.69%), and 91 breakthrough bleeding events in 32 patients were treated with ADYNOVATE. Of these, the treatment was rated as "excellent" for 33 events (36.26%), as "good" for 56 events (61.54%), and as "poor" for 2 events (2.20%). There was no evaluation as "fair."

The 2 breakthrough bleeding events assessed as "poor" occurred in patients who had factor VIII inhibition as a serious adverse drug reaction; therefore, the events were considered to be associated with the impact of inhibitor development.

The hemostatic effectiveness of treatment of breakthrough bleeding during prophylaxis therapy is shown in Table 11.1.2.1-1.

Table 11.1.2.1-1 Hemostatic effectiveness of treatment of breakthrough bleeding (effectiveness analysis set)

Treatment of breakthrough bleeding by the administration of ADYNOVATE	Overall		PTPs		PUPs	
	Number of patients/ events	Percentage (%)	Number of patients/ events	Percentage (%)	Number of patients/ events	Percentage (%)
Number of patients included in efficacy evaluation	131		119		12	
Number of patients receiving prophylaxis therapy	122	93.13	111	93.28	11	91.67
Number of patients with breakthrough bleeding during prophylaxis therapy	35	28.69	32	28.83	3	27.27
Number of breakthrough bleeding events	139		132		7	
Number of patients treated for breakthrough bleeding with ADYNOVATE	32	91.43	29	90.63	3	100.00
Number of breakthrough bleeding events treated with ADYNOVATE	91		86		5	
Efficacy evaluation*: Excellent	33	36.26	32	37.21	1	20.00
Good	56	61.54	54	62.79	2	40.00
Fair	0	0.00	0	0.00	0	0.00
Poor	2	2.20	0	0.00	2	40.00

*For evaluation, the number of events was counted instead of the number of patients.

The most common number of doses required to treat breakthrough bleeding was 1, regardless of the site, severity, or type of bleeding.

The number of doses required to treat breakthrough bleeding and percentage is shown in Table 11.1.2.1-2.

Table 11.1.2.1-2 Number of doses required to treat breakthrough bleeding and percentage (effectiveness analysis set)

Item			Number of doses							
			1		2		3		≥4	
Breakdown of bleeding	Bleeding site	Intraarticular	43	(81.1)	5	(9.4)	4	(7.5)	1	(1.9)
		Intramuscular	14	(87.5)	0	(0.0)	2	(12.5)	0	(0.0)
		Other	16	(72.7)	1	(4.5)	4	(18.2)	1	(4.5)
	Severity of bleeding	Mild	64	(88.9)	4	(5.6)	4	(5.6)	0	(0.0)
		Moderate	8	(47.1)	2	(11.8)	6	(35.3)	1	(5.9)
		Severe	1	(50.0)	0	(0.0)	0	(0.0)	1	(50.0)
	Type of bleeding	Spontaneous bleeding	60	(81.1)	6	(8.1)	6	(8.1)	2	(2.7)
		Traumatic bleeding	13	(76.5)	0	(0.0)	4	(23.5)	0	(0.0)

Hemostatic effectiveness of on-demand replacement therapy

In 17 patients who received on-demand replacement therapy, 61 bleeding events were treated. Of these, the treatment was rated as "excellent" for 20 events (32.79%), as "good" for 36 events (59.02%), as "fair" for 4 events (6.56%), and as "poor" for 1 event (1.64%). The haemophilia A patient in whom treatment was rated as "poor" was old and the number of days of administration of factor VIII products was "0 days." ADYNOVATE was administered 3 times for the treatment of subcutaneous hematoma and hematuria (severity, moderate). Inhibitor development was observed 3

days after the start of the administration of ADYNOVATE for the bleeding concerned, and the administration ended 6 days after the start.

The hemostatic effectiveness of on-demand replacement therapy is shown in Table 11.1.2.2-1.

Table 11.1.2.2-1 Hemostatic effectiveness of on-demand replacement therapy (effectiveness analysis set)

	Overall		PTPs		PUPs	
On-demand replacement therapy	Number of patients/ events	Percentage (%)	Number of patients/ events	Percentage (%)	Number of patients/ events	Percentage (%)
Number of patients included in efficacy evaluation	131		119		12	
Number of patients receiving on-demand replacement therapy	17	12.98	14	11.76	3	25.00
Number of bleeding events	61		58		3	
Efficacy evaluation*: Excellent	20	32.79	19	32.76	1	33.33
Good	36	59.02	35	60.34	1	33.33
Fair	4	6.56	4	6.90	0	0.00
Poor	1	1.64	0	0.00	1	33.33

*For evaluation, the number of events was counted instead of the number of patients.

The most common number of doses required to treat bleeding was 1, regardless of the site, severity, or type of bleeding.

The number of doses required to treat bleeding and percentage are shown in Table 11.1.2.2-2.

Table 11.1.2.2-2 Number of doses required to treat bleeding and percentage (effectiveness analysis set)

Item			Number of doses							
			1		2		3		≥4	
Breakdown of bleeding	Bleeding site	Intraarticular	34	(94.4)	0	(0.0)	1	(2.8)	1	(2.8)
		Intramuscular	4	(80.0)	0	(0.0)	0	(0.0)	1	(20.0)
		Other	15	(75.0)	1	(5.0)	1	(5.0)	3	(15.0)
	Severity of bleeding	Mild	45	(93.8)	1	(2.1)	0	(0.0)	2	(4.2)
		Moderate	3	(50.0)	0	(0.0)	1	(16.7)	2	(33.3)
		Severe	5	(71.4)	0	(0.0)	1	(14.3)	1	(14.3)
	Type of bleeding	Spontaneous bleeding	42	(93.3)	0	(0.0)	2	(4.4)	1	(2.2)
		Traumatic bleeding	11	(68.8)	1	(6.3)	0	(0.0)	4	(25.0)

Efficacy summary

Of the 129 patients included in the efficacy evaluation of prophylaxis therapy, 117 (90.70%) received long-term prophylaxis therapy. Among them, spontaneous bleeding occurred in 20.51% (24/117) of patients and breakthrough bleeding in 27.35% (32/117) of patients. By treatment history, patients who received long-term prophylaxis therapy accounted for 92.44% (110/119 patients) in PTPs and 70.00% (7/10 patients) in PUPs. Among them, spontaneous bleeding occurred in 21.82% (24/110

patients) in PTPs, and breakthrough bleeding occurred in 28.18% (31/110 patients) in PTPs and 14.29% (1/7 patients) in PUPs.

The median annualized rate of spontaneous bleeding was 1.99 times/year (range, 1.00 to 3.59), and the median annualized rate of breakthrough bleeding was 3.09 times/year (range, 1.54 to 5.01).

For the treatment of bleeding, hemostatic effectiveness in the administration for breakthrough bleeding during prophylaxis therapy and on-demand replacement therapy was evaluated. Of the 122 patients who received prophylaxis therapy, 139 breakthrough bleeding events occurred in 35 patients (28.69%), and 91 breakthrough bleeding events in 32 patients were treated with ADYNOVATE. Of these, the treatment was rated as "excellent" for 33 events (36.26%), as "good" for 56 events (61.54%), and as "poor" for 2 events (2.20%). The treatment was rated as "fair" in none of the patients. In 17 patients who received on-demand replacement therapy, 61 bleeding events were treated. Of these, the treatment was rated as "excellent" for 20 events (32.79%), as "good" for 36 events (59.02%), as "fair" for 4 events (6.56%), and as "poor" for 1 event (1.64%).

Safety results

Overall, 135 patients were included in the safety evaluation; 123 were PTPs and 12 were PUPs.

The primary safety outcome in this survey is "inhibitor development" and "shock, anaphylaxis" corresponding to important identified risks in the risk management plan.

Occurrence of Adverse Events

Overall, 10 (7.41%) patients reported 19 AEs. By treatment history, 5 (4.07%) patients in the PTP group and 5 (41.67%) in the PUP group reported AEs.

The only AE reported in ≥2 patients overall was FVIII inhibition with 4 (2.96%) patients; 1 (0.81%) patient in PTPs and 3 (25.0%) patients in PUPs.

Corresponding to primary safety outcome, FVIII inhibition was the only AE reported as the event corresponding to "inhibitor development" (ADYNOVATE Japan drug use-results survey [261601] CSR, Table 10.3.3.1-1). The AEs reported as those corresponding to "shock, anaphylaxis" were dermatitis atopic and eczema, reported in 2 (1.48%) patients, all from the PUP group; 1 (0.74%) patient each had AEs dermatitis atopic and eczema (ADYNOVATE Japan drug use-results survey [261601] CSR, Table 10.3.3.1-2).

The occurrence of adverse events (AEs) is shown in Table 4.

Table 4. Occurrence of Adverse Events (Safety Analysis Set)

	Overall	PTPs	PUPs
Number of patients included in safety evaluation	135	123	12
Number of patients with adverse events	10	5	5
Number of adverse events[a]	19	6	13
Incidence of adverse events, %	7.41	4.07	41.67
Type of adverse event	**Number of patients with adverse events by type (incidence [%])[b]**		
Infections and infestations	2 (1.48)	1 (0.81)	1 (8.33)
Nasopharyngitis	1 (0.74)	0 (0.00)	1 (8.33)
Tonsillitis	1 (0.74)	1 (0.81)	0 (0.00)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.74)	1 (0.81)	0 (0.00)
Hepatic cancer	1 (0.74)	1 (0.81)	0 (0.00)
Blood and lymphatic system disorders	4 (2.96)	1 (0.81)	3 (25.00)
Factor VIII inhibition	4 (2.96)	1 (0.81)	3 (25.00)
Nervous system disorders	1 (0.74)	1 (0.81)	0 (0.00)
Thrombotic cerebral infarction	1 (0.74)	1 (0.81)	0 (0.00)
Respiratory, thoracic and mediastinal disorders	1 (0.74)	1 (0.81)	0 (0.00)
Epistaxis	1 (0.74)	1 (0.81)	0 (0.00)
Gastrointestinal disorders	1 (0.74)	1 (0.81)	0 (0.00)
Discoloured vomit	1 (0.74)	1 (0.81)	0 (0.00)
Skin and subcutaneous tissue disorders	2 (1.48)	0 (0.00)	2 (16.67)
Dermatitis atopic	1 (0.74)	0 (0.00)	1 (8.33)
Eczema	1 (0.74)	0 (0.00)	1 (8.33)
Musculoskeletal and connective tissue disorders	1 (0.74)	0 (0.00)	1 (8.33)
Haemarthrosis	1 (0.74)	0 (0.00)	1 (8.33)
Injury, poisoning and procedural complications	1 (0.74)	0 (0.00)	1 (8.33)
Subcutaneous haematoma	1 (0.74)	0 (0.00)	1 (8.33)

CSR=clinical study report; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; PTP=previously treated patient who had 4 or more exposure days to other products; PUP=previously untreated or minimally treated patient who had 3 or less previous exposure days to other products; SOC=system organ class

[a] Number of adverse events: In cases of multiple occurrences of the same PT in the same patient, the total number of occurrences was counted.

[b] Number of patients with adverse events by type: Multiple occurrences of the same SOC and PT in the same patient were not counted in an overlapping manner.

MedDRA/J version (26.0)

Source: ADYNOVATE Japan drug use-results survey (261601) CSR, Table 10.3.1.1-1

Occurrence of Adverse Drug Reactions/Infections

Overall, 5 (3.70%) patients reported 5 ADRs; 4 (2.96%) patients had FVIII inhibition and 1 (0.74%) patient had a thrombotic cerebral infarction. By treatment history, among PTPs, 2 (1.63%) patients

reported ADRs (1 [0.81%] patient each had FVIII inhibition and thrombotic cerebral infarction); among PUPs, 3 (25.0%) patients reported ADR FVIII inhibition. Among the reported ADRs, FVIII inhibition was expected and thrombotic cerebral infarction was unexpected.

Corresponding to primary safety outcome, FVIII inhibition was the only ADR reported as the event corresponding to "inhibitor development". The ADR was reported as serious in 1 (0.74%) patient and nonserious in 3 (2.22%) patients. The serious ADR of FVIII inhibition was reported in a PUP patient (1 [8.33%] patient). There were no ADRs corresponding to "shock, anaphylaxis."

The occurrence of ADRs/infections (hereinafter, ADRs) is shown in Table 5.

Table 5. Occurrence of Adverse Drug Reactions/Infections (Safety Analysis Set)

	Overall	PTPs	PUPs
Number of patients included in safety evaluation	135	123	12
Number of patients with adverse drug reactions	5	2	3
Number of adverse drug reactions[a]	5	2	3
Incidence of adverse drug reactions, %	3.70	1.63	25.00
Type of adverse drug reactions	**Number of patients with adverse drug reactions by type (incidence [%])[b]**		
Blood and lymphatic system disorders	4 (2.96)	1 (0.81)	3 (25.00)
Factor VIII inhibition	4 (2.96)	1 (0.81)	3 (25.00)
Nervous system disorders	1 (0.74)	1 (0.81)	0 (0.00)
Thrombotic cerebral infarction	1 (0.74)	1 (0.81)	0 (0.00)

CSR=clinical study report; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; PTP=previously treated patient who had 4 or more exposure days to other products; PUP=previously untreated or minimally treated patient who had 3 or less previous exposure days to other products; SOC=system organ class

[a] Number of adverse drug reactions: In cases of multiple occurrences of the same PT in the same patient, the total number of occurrences was counted.

[b] Number of patients with adverse drug reactions by type: Multiple occurrences of the same SOC and PT in the same patient were not counted in an overlapping manner.

MedDRA/J version (26.0)

Source: ADYNOVATE Japan drug use-results survey (261601) CSR, Table 10.3.1.2-1

Serious ADRs of FVIII inhibition and thrombotic cerebral infarction were reported in 1 (0.74%) patient each. An unexpected serious ADR of thrombotic cerebral infarction reported in 1 adult patient (18-64 years old) in the PTP group was resolved during continued treatment with ADYNOVATE and did not recur after that; thus, it was considered to be attributable to a complication of hypertension and not to be causally related to ADYNOVATE. A serious ADR of FVIII inhibition was reported in a young child in the PUP group and the outcome was not resolved. This pediatric patient had no past history, complications, history of allergy, or family history of inhibitor development while receiving treatment with ADYNOVATE. Severe FVIII inhibition (verbatim term, FVIII inhibitor development) was observed during prophylaxis therapy using ADYNOVATE (500 IU twice weekly). After the development of inhibitor was confirmed in the results of a blood test performed, the inhibitor level increased. Prophylaxis therapy using ADYNOVATE ended, and the treatment was shifted to immune-tolerance therapy using ADYNOVATE. The administration of ADYNOVATE was continued at an increased dose (the dose was increased to 750, 1000, and 1500 IU, and twice-weekly administration was continued). The inhibitor level gradually declined but stopped declining once it reached 8 Bethesda Units. Thus, ADYNOVATE was discontinued.

Occurrence of ADRs by time of onset and outcome: The time of onset of FVIII inhibition was from Day 16 to Day 30 in 2 (1.48%) patients, Day 31 to Day 60 and Day 91 to Day 135 in 1 (0.74%) patient each. The time of onset of thrombotic cerebral infarction was from Day 181 to Day 270 in 1 (0.74%) patient. The outcome of FVIII inhibition was resolved in 2 (1.48%) patients, resolving in 1 (0.74%) patient, and not resolved in 1 (0.74%) patient. The outcome of thrombotic cerebral infarction was resolved in 1 (0.74%) patient.

Occurrence of ADRs by age group: FVIII inhibition was reported in 2 (5.71%) patients aged <12 years and 2 (2.50%) patients aged 18-64 years. Thrombotic cerebral infarction was reported in 1 (1.25%) patient aged 18-64 years. In PTPs, FVIII inhibition and thrombotic cerebral infarction were reported in 1 (1.30%) patient each aged 18-64 years. In PUPs, FVIII inhibition was reported in 2 (33.33%) patients aged <12 years and 1 (33.33%) patient aged 18-64 years; no thrombotic cerebral infarction occurred.

Occurrence of ADRs by patient background and treatment factor: The incidence of ADRs by the number of days of administration of FVIII preparation before the administration of ADYNOVATE (cumulative) was 25.0% (3/12 patients) for 0-3 days, 0% for 4-50 days, 0% for 51-150 days, and 1.83% (2/109 patients) for 151 or more days.

The incidence of ADRs by gender was 2.99% (4/134 patients) in males and 100.0% (1/1 patient) in females. The incidence of ADRs by cause of hemophilia A was 3.70% (5/135 patients) for congenital disease and 0% for acquired disease.

The incidence of ADRs by age at the time of diagnosis of hemophilia A was 0% for <1 year, 6.45% (2/31 patients) for ≥1 and <12 years, 25.0% (1/4 patients) for ≥12 and <18 years, 14.29% (1/7 patients) for ≥18 and <65 years, 0% for ≥65 years, and 2.0% (1/50 patients) for unknown at the time of diagnosis. The incidence of ADRs by most recent ABR was 0% for 0 to <1 times/year, 2.27% (1/44 patients) for 1 to <10 times/year, 7.14% (1/14 patients) for ≥10 times/year, and 6.82% (3/44 patients) for unknown. The incidence of ADRs by details of treatment was 3.39% (4/118 patients) for prophylaxis therapy, 0% for on-demand replacement therapy, and 12.50% (1/8 patients) for prophylaxis therapy and on-demand replacement therapy (patients whose therapy was changed during the observation period).

Assessor's comment

ADRs were reported in 2 paediatric patients. Both events were FVIII inhibition in previously untreated patients under the age of 12. No ADRs were reported in adolescent patients.

In the adult patient population, FVIII inhibition was reported in two patients and thrombotic cerebral infarction was reported in one patient.

No concerns arise from the limited data presented, however, separate analyses, including summary tables, according to paediatric age subpopulations are requested.

Safety Summary

Of the 135 patients included in the safety evaluation, 123 were PTPs and 12 were PUPs.

Overall, 5 ADRs were reported in 5 (3.70%) patients. The reported ADRs included FVIII inhibition in 4 (2.96%) patients (2 [5.71%] patients aged <12 years and 2 [2.50%] patients aged 18-64 years) and thrombotic cerebral infarction in 1 (0.74%) patient aged 18 to 64 years. Of these, FVIII inhibition and thrombotic cerebral infarction in 1 patient each were reported as serious.

A serious ADR of FVIII inhibition was reported in a young child in the PUP group and the outcome was not resolved.

An unexpected ADR, "thrombotic cerebral infarction," was observed, but resolved during continued treatment with ADYNOVATE and did not recur after that; thus, the sponsor considered to be attributable to a complication of hypertension and not to be causally related (reported and analyzed) to ADYNOVATE. Based on the above, no information showing changes in the safety profile of ADYNOVATE has been obtained, and therefore, it was judged unnecessary to take new safety measures at this point in time.

2.3.2. Discussion on clinical aspects

The MAH provided results from the completed Adynovate drug use-results survey, study 26101, which was conducted in Japan to investigate the safety and efficacy of Adynovate in actual use in daily clinical practice. The study included patients <18 years of age and was therefore submitted to comply with the requirements as stipulated in Article 46 of the Paediatric Regulation.

Study 261601 was conducted to gather data on real-world evidence on safety and efficacy of Adynovate use in Japan.

Eligible participants were HA patients who received Adynovate in the real-world clinical setting, including both PTPs (≥4 EDs to other products) and PUPs (previously untreated or minimally treated patients who had ≤3 EDs to other products).

In total, 135 paediatric and adult patients from 66 medical institutions were registered into the study. Regarding the paediatric study population, 35 (25.3%) patients were under 12 years of age, including 6 PUPs. 5 (3.7%) patients were ≥12 and <18 years of age, including 1 PUP.

No study documentation beyond the final study report were provided, since according to the MAH no English translation was prepared. Therefore, neither study protocol nor SAP were available for review. No individual patient listings or narratives were provided. While clearly limiting the interpretability of the provided data, this issue is not further pursued due to the exploratory character of the submitted survey.

ADRs were reported in 2 paediatric patients. Both events were FVIII inhibition in previously untreated patients under the age of 12. No ADRs were reported in adolescent patients.

In the adult patient population, FVIII inhibition was reported in two patients and thrombotic cerebral infarction was reported in one patient.

No concerns arise from the limited data presented, however, data were initially presented for the overall study population, including adults. Therefore separate analyses according to paediatric age subpopulations were requested. With the responses, the Applicant provided separate analyses, which did not raise concerns (see assessment of response to question 1 below, section 4).

Overall, from the data provided, no update to the PI is deemed necessary.

3. CHMP overall conclusion and recommendation

☒ Not fulfilled:

Based on the data submitted, the MAH should provide additional analyses for the paediatric study population as part of this procedure. (see section "Request for supplementary information")

4. Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. Separate analyses for the paediatric study population are requested, including baseline characteristics, efficacy, and safety analyses.

The timetable is a 30 day response timetable with clock stop.

MAH responses to Request for supplementary information

Patient Composition

The pediatric population enrolled in Study 261601 included 13 patients aged <6 years, 22 patients aged 6 to <12 years and 5 patients aged 12 to <18 years. All pediatric patients were male, Asian, and were confirmed to have congenital hemophilia A. Overall, 4 pediatric patients (10.00%) had a history of serious bleeding (2 patients [15.38%] aged <6 years and 2 patients [9.09%] aged 6 to <12 years), and 7 pediatric patients (17.50%) had a surgical history (4 patients [30.77%] aged <6 years and 3 patients [13.64%] aged 6 to <12 years) (Table 1.a).

Overall, history of factor VIII (FVIII) inhibitor development was reported for 5 pediatric patients (12.50%; 1 patient [7.69%] aged <6 years and 4 patients [18.18%] aged 6 to <12 years). History of FVIII inhibitor development was unknown for 4 pediatric patients (10.00%; 2 patients [15.38%] aged <6 years, 1 patient [4.55%] aged 6 to <12 years, and 1 patient [20.00%] aged 12 to <18 years). Before the start of administration of Adynovate, the majority of pediatric patients received prophylaxis therapy (24 patients [60.00%]) or prophylaxis and on-demand replacement therapy (9 patients [22.50%]). The majority of pediatric patients had a cumulative number of days of administration of FVIII products before the administration of Adynovate of at least 151 days (28 patients [70.00%]) (Table 1.a).

Table 1.a Baseline Characteristics of the Study Population by Pediatric Sub-Population and Overall Pediatric Population (Safety Analysis Set)

	Overall (Pediatric patients) (N=40)		<6 years (N=13)		6-<12 years (N=22)		12-<18 years (N=5)	
	n	%	n	%	n	%	n	%
History of treatment with factor VIII products before administration of Adynovate								
4 or more days of administration (PTPs)	33	82.50	7	53.85	22	100.00	4	80.00
3 or less days of administration (PUPs)	7	17.50	6	46.15	0	0.00	1	20.00
Unknown	0	0.00	0	0.00	0	0.00	0	0.00
Number of days of administration of factor VIII products before the administration of Adynovate (cumulative)								
0 to 3 days	7	17.50	6	46.15	0	0.00	1	20.00
4 to 50 days	2	5.00	1	7.69	1	4.55	0	0.00
51 to 150 days	2	5.00	2	15.38	0	0.00	0	0.00
≥151 days	28	70.00	4	30.77	21	95.45	3	60.00
Number of days of administration unknown	1	2.50	0	0.00	0	0.00	1	20.00
Gender								
Male	40	100.00	13	100.00	22	100.00	5	100.00
Female	0	0.00	0	0.00	0	0.00	0	0.00

Table 1.a Baseline Characteristics of the Study Population by Pediatric Sub-Population and Overall Pediatric Population (Safety Analysis Set)

	Overall (Pediatric patients) (N=40)		<6 years (N=13)		6-<12 years (N=22)		12-<18 years (N=5)	
	n	%	n	%	n	%	n	%
Age (years)								
<12	35	87.50	13	100.00	22	100.00	0	0.00
≥12 and <18	5	12.50	0	0.00	0	0.00	5	100.00
≥18 and <65	0	0.00	0	0.00	0	0.00	0	0.00
≥65	0	0.00	0	0.00	0	0.00	0	0.00
Unknown (date of birth and age cannot be provided)	0	0.00	0	0.00	0	0.00	0	0.00
Medical care category								
Inpatient	5	12.50	5	38.46	0	0.00	0	0.00
Outpatient	35	87.50	8	61.54	22	100.00	5	100.00
Race								
Asian	40	100.00	13	100.00	22	100.00	5	100.00
White	0	0.00	0	0.00	0	0.00	0	0.00
Black	0	0.00	0	0.00	0	0.00	0	0.00
Other	0	0.00	0	0.00	0	0.00	0	0.00
Serious bleeding								
No	36	90.00	11	84.62	20	90.91	5	100.00
Yes	4	10.00	2	15.38	2	9.09	0	0.00
Unknown	0	0.00	0	0.00	0	0.00	0	0.00

Table 1.a Baseline Characteristics of the Study Population by Pediatric Sub-Population and Overall Pediatric Population (Safety Analysis Set)

	Overall (Pediatric patients) (N=40)		<6 years (N=13)		6-<12 years (N=22)		12-<18 years (N=5)	
	n	%	n	%	n	%	n	%
Surgical history								
No	32	80.00	9	69.23	19	86.36	4	80.00
Yes	7	17.50	4	30.77	3	13.64	0	0.00
Unknown	1	2.50	0	0.00	0	0.00	1	20.00
Past history								
No	36	90.00	12	92.31	19	86.36	5	100.00
Yes	4	10.00	1	7.69	3	13.64	0	0.00
Unknown	0	0.00	0	0.00	0	0.00	0	0.00
Breakdown of past history (overlapping tabulation)								
Hepatitis C	0	0.00	0	0.00	0	0.00	0	0.00
Hepatitis B	0	0.00	0	0.00	0	0.00	0	0.00
Other	4	10.00	1	7.69	3	13.64	0	0.00
Complications								
No	37	92.50	11	84.62	21	95.45	5	100.00
Yes	2	5.00	1	7.69	1	4.55	0	0.00
Unknown	1	2.50	1	7.69	0	0.00	0	0.00
Breakdown of complications (overlapping tabulation)								
HIV infection	0	0.00	0	0.00	0	0.00	0	0.00
Hypertension	0	0.00	0	0.00	0	0.00	0	0.00
Hyperlipidemia	0	0.00	0	0.00	0	0.00	0	0.00
Diabetes mellitus	0	0.00	0	0.00	0	0.00	0	0.00

Table 1.a Baseline Characteristics of the Study Population by Pediatric Sub-Population and Overall Pediatric Population (Safety Analysis Set)

	Overall (Pediatric patients) (N=40)		<6 years (N=13)		6-<12 years (N=22)		12-<18 years (N=5)	
	n	%	n	%	n	%	n	%
Gastric ulcer	0	0.00	0	0.00	0	0.00	0	0.00
Chronic gastritis	0	0.00	0	0.00	0	0.00	0	0.00
Anemia	1	2.50	1	7.69	0	0.00	0	0.00
Epilepsy	0	0.00	0	0.00	0	0.00	0	0.00
Depression	0	0.00	0	0.00	0	0.00	0	0.00
Insomnia	0	0.00	0	0.00	0	0.00	0	0.00
Other	1	2.50	0	0.00	1	4.55	0	0.00
Hemophilic arthropathy								
No	38	95.00	12	92.31	21	95.45	5	100.00
Yes	1	2.50	0	0.00	1	4.55	0	0.00
Unknown	1	2.50	1	7.69	0	0.00	0	0.00
Target joint								
No	38	95.00	12	92.31	21	95.45	5	100.00
Yes	1	2.50	0	0.00	1	4.55	0	0.00
Unknown	1	2.50	1	7.69	0	0.00	0	0.00
Hepatic impairment								
No	40	100.00	13	100.00	22	100.00	5	100.00
Yes	0	0.00	0	0.00	0	0.00	0	0.00
Unknown	0	0.00	0	0.00	0	0.00	0	0.00

Table 1.a Baseline Characteristics of the Study Population by Pediatric Sub-Population and Overall Pediatric Population (Safety Analysis Set)

	Overall (Pediatric patients) (N=40)		<6 years (N=13)		6-<12 years (N=22)		12-<18 years (N=5)	
	n	%	n	%	n	%	n	%
Breakdown of hepatic impairment (overlapping tabulation)								
Hepatitis C	0	0.00	0	0.00	0	0.00	0	0.00
Hepatitis B	0	0.00	0	0.00	0	0.00	0	0.00
Cirrhosis	0	0.00	0	0.00	0	0.00	0	0.00
Fatty liver	0	0.00	0	0.00	0	0.00	0	0.00
Other	0	0.00	0	0.00	0	0.00	0	0.00
Renal impairment								
No	40	100.00	13	100.00	22	100.00	5	100.00
Yes	0	0.00	0	0.00	0	0.00	0	0.00
Unknown	0	0.00	0	0.00	0	0.00	0	0.00
Breakdown of renal impairment (overlapping tabulation)								
Diabetic nephropathy	0	0.00	0	0.00	0	0.00	0	0.00
Renal calculus	0	0.00	0	0.00	0	0.00	0	0.00
Other	0	0.00	0	0.00	0	0.00	0	0.00
Allergy								
No	37	92.50	12	92.31	20	90.91	5	100.00
Yes	3	7.50	1	7.69	2	9.09	0	0.00
Unknown	0	0.00	0	0.00	0	0.00	0	0.00

Table 1.a Baseline Characteristics of the Study Population by Pediatric Sub-Population and Overall Pediatric Population (Safety Analysis Set)

	Overall (Pediatric patients) (N=40)		<6 years (N=13)		6-<12 years (N=22)		12-<18 years (N=5)	
	n	%	n	%	n	%	n	%
Breakdown of allergy (overlapping tabulation)								
Drug	0	0.00	0	0.00	0	0.00	0	0.00
Food	2	5.00	1	7.69	1	4.55	0	0.00
Pollen	0	0.00	0	0.00	0	0.00	0	0.00
Other	1	2.50	0	0.00	1	4.55	0	0.00
Cause of hemophilia A								
Congenital	40	100.00	13	100.00	22	100.00	5	100.00
Acquired	0	0.00	0	0.00	0	0.00	0	0.00
Age at hemophilia A diagnosis (years)								
<1	23	57.50	8	61.54	13	59.09	2	40.00
≥1 and <12	15	37.50	5	38.46	8	36.36	2	40.00
≥12 and <18	1	2.50	0	0.00	0	0.00	1	20.00
≥18 and <65	0	0.00	0	0.00	0	0.00	0	0.00
≥65	0	0.00	0	0.00	0	0.00	0	0.00
Unknown	1	2.50	0	0.00	1	4.55	0	0.00
Most recent annualized bleeding rate (times/year)								
≥0 and <1	12	30.00	2	15.38	8	36.36	2	40.00
≥1 and <10	14	35.00	4	30.77	9	40.91	1	20.00
≥10	2	5.00	1	7.69	1	4.55	0	0.00
Unknown	12	30.00	6	46.15	4	18.18	2	40.00

Table 1.a Baseline Characteristics of the Study Population by Pediatric Sub-Population and Overall Pediatric Population (Safety Analysis Set)

	Overall (Pediatric patients) (N=40)		<6 years (N=13)		6-<12 years (N=22)		12-<18 years (N=5)	
	n	%	n	%	n	%	n	%
Severity of hemophilia A (plasma residual factor VIII activity)								
Severe (<1%)	34	85.00	12	92.31	17	77.27	5	100.00
Moderate (≥1% to <5%)	5	12.50	1	7.69	4	18.18	0	0.00
Mild (≥5%)	0	0.00	0	0.00	0	0.00	0	0.00
Unknown (measured value unknown or not measured)	1	2.50	0	0.00	1	4.55	0	0.00
Status of administration of factor VIII products before the start of administration of Adynovate (most recent)								
Kovaltry	1	2.50	0	0.00	1	4.55	0	0.00
Eloctate	1	2.50	0	0.00	1	4.55	0	0.00
NovoEight	0	0.00	0	0.00	0	0.00	0	0.00
Advate	33	82.50	9	69.23	20	90.91	4	80.00
Kogenate FS	0	0.00	0	0.00	0	0.00	0	0.00
Cross eight M/MC	0	0.00	0	0.00	0	0.00	0	0.00
Confact F	0	0.00	0	0.00	0	0.00	0	0.00
Other	0	0.00	0	0.00	0	0.00	0	0.00
Not performed	5	12.50	4	30.77	0	0.00	1	20.00

Table 1.a Baseline Characteristics of the Study Population by Pediatric Sub-Population and Overall Pediatric Population (Safety Analysis Set)

	Overall (Pediatric patients) (N=40)		<6 years (N=13)		6-<12 years (N=22)		12-<18 years (N=5)	
	n	%	n	%	n	%	n	%
Dosing regimen before the start of administration of Adynovate (most recent)								
Prophylaxis therapy	24	60.00	5	38.46	16	72.73	3	60.00
On-demand replacement therapy	1	2.50	1	7.69	0	0.00	0	0.00
Prophylaxis and on-demand replacement therapy	9	22.50	2	15.38	6	27.27	1	20.00
Other	1	2.50	1	7.69	0	0.00	0	0.00
Not performed	5	12.50	4	30.77	0	0.00	1	20.00
History of factor VIII inhibitor development								
No	31	77.50	10	76.92	17	77.27	4	80.00
Yes	5	12.50	1	7.69	4	18.18	0	0.00
Unknown	4	10.00	2	15.38	1	4.55	1	20.00
Family history of hemophilia								
No	24	60.00	8	61.54	14	63.64	2	40.00
Yes	13	32.50	4	30.77	7	31.82	2	40.00
Unknown	3	7.50	1	7.69	1	4.55	1	20.00
Family history of inhibitor development								
No	32	80.00	10	76.92	19	86.36	3	60.00
Yes	2	5.00	2	15.38	0	0.00	0	0.00
Unknown	6	15.00	1	7.69	3	13.64	2	40.00

Table 1.a Baseline Characteristics of the Study Population by Pediatric Sub-Population and Overall Pediatric Population (Safety Analysis Set)

	Overall (Pediatric patients) (N=40)		<6 years (N=13)		6-<12 years (N=22)		12-<18 years (N=5)	
	n	%	n	%	n	%	n	%
Pregnancy								
No	0	0.00	0	0.00	0	0.00	0	0.00
Yes	0	0.00	0	0.00	0	0.00	0	0.00
Concomitant drugs								
No	33	82.50	7	53.85	21	95.45	5	100.00
Yes	7	17.50	6	46.15	1	4.55	0	0.00
Concomitant therapies								
No	40	100.00	13	100.00	22	100.00	5	100.00
Yes	0	0.00	0	0.00	0	0.00	0	0.00

N: number of patients included in safety evaluation; PTP: previously treated patient; PUP: previously untreated patient.

Performed Therapy

The breakdown of major therapies using Adynovate was prophylaxis therapy performed in 38 pediatric patients (95.0%), including 31 pediatric previously treated patients (PTPs) and 7 pediatric previously untreated patients (PUPs) (100.0%); on-demand replacement therapy was not performed in pediatric patients (Table 1.b).

Prophylaxis therapy and on-demand replacement therapy were performed in 2 pediatric patients (5.0%), both were PTPs (6.1%); they were patients whose therapy was changed during the observation period (Table 1.b).

Table 1.b Status of Administration of Adynovate at the End of the Observation Period (Safety Analysis Set)

	Overall (Pediatric patients) (N=40) n (%)		PTPs (N=33) n (%)		PUPs (N=7) n (%)	
Major therapies using Adynovate						
Prophylaxis therapy	38	(95.0)	31	(93.9)	7	(100.0)
On-demand replacement therapy	0	(0.0)	0	(0.0)	0	(0.0)
Prophylaxis and on-demand replacement therapies*	2	(5.0)	2	(6.1)	0	(0.0)

N: number of patients included in safety evaluation; PTP: previously treated patient; PUP: previously untreated patient.

*Patients whose therapy was changed during the observation period.

Type of Prophylaxis Therapy

The majority of pediatric patients (39 [97.5%]) received long-term prophylaxis therapy and 2 pediatric patients (5.0%), both aged <6 years, received short-term prophylaxis; 1 of these pediatric patient aged <6 years received both short- and long-term prophylaxis (Table 1.c).

Table 1.c Types of Prophylaxis Therapy (Safety Analysis Set)

	Overall (Pediatric patients) (N=40) n (%)		<6 years (N=13) n (%)		6-<12 years (N=22) n (%)		12-<18years (N=5) n (%)	
Long-term prophylaxis	39*	(97.5)	12*	(92.3)	22	(100.0)	5	(100.0)
Short-term prophylaxis	2*	(5.0)	2*	(15.4)	0	(0.0)	0	(0.0)
Preventive treatment	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

N: number of patients included in safety evaluation.

*One patient who received both long-term and short-term therapies was counted in each of these categories.

Details of Treatment (Long-Term Prophylaxis Therapy)

The mean (standard deviation [SD]) duration of long-term prophylaxis therapy for pediatric patients was 358.8 (103.94) days overall, with 349.4 (144.65) days in patients aged <6 years, 354.5 (40.58) days in patients aged 6 to <12 years, and 398.4 (191.52) days in patients aged 12 to <18 years. The mean (SD) dose per administration was 50.9 (11.11) IU/kg for pediatric patients overall (52.3 [9.64]

IU/kg for patients aged <6 years, 52.2 [11.55] IU/kg for patients aged 6 to <12 years, and 41.6 [9.17] IU/kg for patients aged 12 to <18 years). The mean (SD) dosing frequency was 2.1 (0.24) times per week for the pediatric patients overall (2.0 [0.00] times per week for patients aged <6 years, 2.1 [0.22] times per week for patients aged 6 to <12 years, and 2.2 [0.45] times per week for patients aged 12 to <18 years) (Table 1.d).

Table 1.d Details of Treatment (Long-Term Prophylaxis Therapy) (Safety Analysis Set)

Item	Overall (Pediatric patients) (N=38*)	<6 years (N=11*)	6-<12 years (N=22)	12-<18 years (N=5)
Duration of treatment (days)				
Mean	358.8	349.4	354.5	398.4
Standard deviation	103.94	144.65	40.58	191.52
Minimum	179	192	189	179
First quartile	349.0	251.0	356.0	366.0
Median	365.5	363.0	366.0	367.0
Third quartile	370.0	370.0	368.0	372.0
Maximum	726	726	389	708

Table 1.d Details of Treatment (Long-Term Prophylaxis Therapy) (Safety Analysis Set)

Item	Overall (Pediatric patients) (N=38*)	<6 years (N=11*)	6-<12 years (N=22)	12-<18 years (N=5)
Dose per administration (IU/kg)				
Mean	50.9	52.3	52.2	41.6
Standard deviation	11.11	9.64	11.55	9.17
Minimum	23	37	23	26
First quartile	45.9	46.3	47.5	41.5
Median	49.6	50.4	51.1	44.7
Third quartile	57.6	56.8	58.8	46.1
Maximum	79	74	79	50
Dosing frequency (times per week)				
Mean	2.1	2.0	2.1	2.2
Standard deviation	0.24	0.00	0.22	0.45
Minimum	2	2	2	2
First quartile	2.0	2.0	2.0	2.0
Median	2.0	2.0	2.0	2.0
Third quartile	2.0	2.0	2.0	2.0
Maximum	3	2	3	3
Total number of doses				
Mean	108.9	106.5	107.4	120.6
Standard deviation	33.17	46.11	15.17	58.76
Minimum	47	54	92	47
First quartile	96.0	70.0	96.0	99.0
Median	104.0	106.0	104.0	104.0
Third quartile	119.0	119.0	109.0	150.0
Maximum	217	217	140	203

N: number of patients included in safety evaluation.

*In 1 patient, "long-term" was selected, but the details of treatment was "immune-tolerance therapy"; therefore, this patient was excluded from tabulation.

Details of Treatment (Short-Term Prophylaxis Therapy)

The pediatric patient who received short-term prophylaxis therapy was a PUP aged <6 years. The patient's duration of treatment was 53.0 days, the dose per administration was 48.4 IU/kg, and the total number of doses was 15.0 (Table 1.e).

Table 1.e Details of Treatment (Short-Term Prophylaxis Therapy) (Safety Analysis Set)

Item	Overall (Pediatric patients) (N=1*)	PTPs (N=0)	PUPs** (N=1*)
Duration of treatment (days)			
Mean	53.0	-	53.0
Standard deviation	-	-	-
Minimum	53	-	53
First quartile	53.0	-	53.0
Median	53.0	-	53.0
Third quartile	53.0	-	53.0
Maximum	53	-	53
Dose per administration (IU/kg)			
Mean	48.4	-	48.4
Standard deviation	-	-	-
Minimum	48	-	48
First quartile	48.4	-	48.4
Median	48.4	-	48.4
Third quartile	48.4	-	48.4
Maximum	48	-	48
Dosing frequency (times per week)			
Mean	-	-	-
Standard deviation	-	-	-
Minimum	-	-	-
First quartile	-	-	-
Median	-	-	-
Third quartile	-	-	-
Maximum	-	-	-

Table 1.e Details of Treatment (Short-Term Prophylaxis Therapy) (Safety Analysis Set)

Item	Overall (Pediatric patients) (N=1*)	PTPs (N=0)	PUPs** (N=1*)
Total number of doses			
Mean	15.0	-	15.0
Standard deviation	-	-	-
Minimum	15	-	15
First quartile	15.0	-	15.0
Median	15.0	-	15.0
Third quartile	15.0	-	15.0
Maximum	15	-	15

N: number of patients included in safety evaluation; PTP: previously treated patient; PUP: previously untreated patient

*In 1 patient, "long-term" was selected, but the details of treatment was "immune-tolerance therapy"; therefore, this patient was excluded from tabulation.

**<6 years patient.

Details of Treatment (On-Demand Replacement Therapy)

A total of 2 bleeding events occurring in 2 pediatric patients (1 patient aged <6 years and 1 patient aged 6 to <12 years) were treated with on-demand replacement therapy. The site of bleeding was intramuscular for the patient aged 6 to < 12 years and other for the patient aged <6 years. Both bleeding events were of mild severity and were traumatic bleeding.

The mean duration of on-demand replacement therapy was 5.5 days for pediatric patients (10.0 days for the patient aged <6 years and 1.0 for the patient aged 6 to <12 years); the mean dose per administration and mean number of doses were 63.5 IU/kg and 4.5 doses, respectively, for pediatric patients (Table 1.f).

Table 1.f Details of Treatment (On-Demand Replacement Therapy) (Safety Analysis Set)

Item		Overall (Pediatric patients) (N=2)		<6 years (N=1)		6-<12 years (N=1)		12-<18 years (N=0)	
Number of bleeding events		2		1		1		0	
Breakdown of bleeding									
		n	%	n	%	n	%	n	%
Bleeding site	Intraarticular	0	(0.0)	0	(0.0)	0	(0.0)	0	-
	Intramuscular	1	(50.0)	0	(0.0)	1	(100.0)	0	-
	Other	1	(50.0)	1	(100.0)	0	(0.0)	0	-
Severity of bleeding	Mild	2	(100.0)	1	(100.0)	1	(100.0)	0	-
	Moderate	0	(0.0)	0	(0.0)	0	(0.0)	0	-
	Severe	0	(0.0)	0	(0.0)	0	(0.0)	0	-
Type of bleeding	Spontaneous bleeding	0	(0.0)	0	(0.0)	0	(0.0)	0	-
	Traumatic bleeding	2	(100.0)	1	(100.0)	1	(100.0)	0	-
Duration of treatment (days)									
Mean		5.5		10.0		1.0		-	
Standard deviation		6.36		-		-		-	
Minimum		1		10		1		-	
First quartile		1.0		10.0		1.0		-	
Median		5.5		10.0		1.0		-	
Third quartile		10.0		10.0		1.0		-	
Maximum		10		10		1		-	
Dose per administration (IU/kg)									
Mean		63.5		69.8		57.1		-	
Standard deviation		8.97		-		-		-	
Minimum		57		70		57		-	
First quartile		57.1		69.8		57.1		-	
Median		63.5		69.8		57.1		-	
Third quartile		69.8		69.8		57.1		-	
Maximum		70		70		57		-	

Table 1.f Details of Treatment (On-Demand Replacement Therapy) (Safety Analysis Set)

Item	Overall (Pediatric patients) (N=2)	<6 years (N=1)	6-<12 years (N=1)	12-<18 years (N=0)
Number of doses (times)				
Mean	4.5	8.0	1.0	-
Standard deviation	4.95	-	-	-
Minimum	1	8	1	-
First quartile	1.0	8.0	1.0	-
Median	4.5	8.0	1.0	-
Third quartile	8.0	8.0	1.0	-
Maximum	8	8	1	-

N: number of patients included in safety evaluation.

Occurrence of Adverse Events

The incidence of adverse events (AEs) in pediatric patients was 12.50% (30.77% in patients aged <6 years, 4.55% in patients aged 6 to <12 years, and 0.00% in patients aged 12 to <18 years). One serious AE of FVIII inhibition was reported for a pediatric patient aged <6 years. Other AEs reported were non-serious and were reported by no more than 1 pediatric patient (Table 1.g).

Table 1.g Occurrence of Adverse Events (Safety Analysis Set)

	Overall (Pediatric patients) (N=40)				<6 years (N=13)				6-<12 years (N=22)				12-<18 years (N=5)			
Number of patients with AEs	5				4				1				0			
Number of AEs	14				12				2				0			
Incidence of AEs	12.50%				30.77%				4.55%				0.00%			
Type of AE	Seriousness				Seriousness				Seriousness				Seriousness			
	Serious		Non-Serious		Serious		Non-Serious		Serious		Non-Serious		Serious		Non-Serious	
Infections and infestations	0	(0.00)	1	(2.50)	0	(0.00)	1	(7.69)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)
Nasopharyngitis	0	(0.00)	1	(2.50)	0	(0.00)	1	(7.69)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)
Blood and lymphatic system disorders	1	(2.50)	1	(2.50)	1	(7.69)	1	(7.69)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)
Factor VIII inhibition	1	(2.50)	1	(2.50)	1	(7.69)	1	(7.69)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)
Respiratory, thoracic and mediastinal disorders	0	(0.00)	1	(2.50)	0	(0.00)	0	(0.00)	0	(0.00)	1	(4.55)	0	(0.00)	0	(0.00)
Epistaxis	0	(0.00)	1	(2.50)	0	(0.00)	0	(0.00)	0	(0.00)	1	(4.55)	0	(0.00)	0	(0.00)
Gastrointestinal disorders	0	(0.00)	1	(2.50)	0	(0.00)	0	(0.00)	0	(0.00)	1	(4.55)	0	(0.00)	0	(0.00)
Discoloured vomit	0	(0.00)	1	(2.50)	0	(0.00)	0	(0.00)	0	(0.00)	1	(4.55)	0	(0.00)	0	(0.00)
Skin and subcutaneous tissue disorders	0	(0.00)	2	(5.00)	0	(0.00)	2	(15.38)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)
Dermatitis atopic	0	(0.00)	1	(2.50)	0	(0.00)	1	(7.69)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)
Eczema	0	(0.00)	1	(2.50)	0	(0.00)	1	(7.69)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)
Musculoskeletal and connective tissue disorders	0	(0.00)	1	(2.50)	0	(0.00)	1	(7.69)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)

Table 1.g Occurrence of Adverse Events (Safety Analysis Set)

	Overall (Pediatric patients) (N=40)				<6 years (N=13)				6-<12 years (N=22)				12-<18 years (N=5)			
Haemarthrosis	0	(0.00)	1	(2.50)	0	(0.00)	1	(7.69)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)
Injury, poisoning and procedural complications	0	(0.00)	1	(2.50)	0	(0.00)	1	(7.69)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)
Subcutaneous haematoma	0	(0.00)	1	(2.50)	0	(0.00)	1	(7.69)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)

AE: adverse event; N: number of patients included in safety evaluation; PT: Preferred Term; SOC: System Organ Class.

Number of AEs: In cases of multiple occurrences of the same PT in the same patient, the total number of occurrences is counted.

Number of patients with AEs by type: Multiple occurrences of the same SOC and PT in the same patient are not counted in an overlapping manner.

Incidence of AEs=number of patients with AEs / N × 100

Occurrence of Adverse Drug Reactions/Infections

The incidence of adverse drug reactions/infections in pediatric patients was 5.00%; 2 patients, both aged <6 years reported 2 adverse drug reactions/infections (FVIII inhibition). One of the event was considered serious, the other was not serious (Table 1.h).

Table 1.h Occurrence of Adverse Drug Reactions/Infections

	Overall (Pediatric patients) (N=40)				<6 years (N=13)				6-<12 years (N=22)				12-<18 years (N=5)			
Number of patients with AEs	2				2				0				0			
Number of AEs	2				2				0				0			
Incidence of AEs	5.00%				15.38%				0.00%				0.00%			
Type of AE	Seriousness				Seriousness				Seriousness				Seriousness			
	Serious		Non-Serious		Serious		Non-Serious		Serious		Non-Serious		Serious		Non-Serious	
Blood and lymphatic system disorders	1	(2.50)	1	(2.50)	1	(7.69)	1	(7.69)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)
Factor VIII inhibition	1	(2.50)	1	(2.50)	1	(7.69)	1	(7.69)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)

AE: adverse event; N: number of patients included in safety evaluation; PT: Preferred Term; SOC: System Organ Class.

Number of AEs: In cases of multiple occurrences of the same PT in the same patient, the total number of occurrences is counted.

Number of patients with AEs by type: Multiple occurrences of the same SOC and PT in the same patient are not counted in an overlapping manner.

Occurrence of Adverse Drug Reactions/Infections by Patient Background and Treatment Factor

Adverse drug reactions/infections were reported by 2 pediatric patients aged <12 years; both were PUPs with 3 or less days of administration of FVIII (incidence: 28.57%). Both pediatric patients were outpatients with no history of serious bleeding, and no surgical history; their most recent annualized bleeding rate (ABR) was unknown. Both had severe hemophilia A (Table 1.i).

Table 1.i Occurrence of Adverse Drug Reactions/Infections by Patient Background and Treatment Factor (Overall Pediatric Patients) (Safety Analysis Set)

Patient background item Levels	Number of patients	Number of patients with adverse drug reactions	Incidence %
Number of patients included in safety evaluation	40	2	5.00
History of treatment with factor VIII products before administration of Adynovate			
4 or more days of administration (PTPs)	33	0	0.00
3 or less days of administration (PUPs)	7	2	28.57
Unknown	0	0	-
Number of days of administration of factor VIII products before the administration of Adynovate (cumulative)			
0 to 3 days	7	2	28.57
4 to 50 days	2	0	0.00
51 to 150 days	2	0	0.00
≥151 days	28	0	0.00
Number of days of administration unknown	1	0	0.00
Gender			
Male	40	2	5.00
Female	0	0	-
Age (years)			
<12	35	2	5.71
≥12 and <18	5	0	0.00
≥18 and <65	0	0	-
≥65	0	0	-
Unknown (date of birth and age cannot be provided)	0	0	-
Medical care category			
Inpatient	5	0	0.00
Outpatient	35	2	5.71

Table 1.i Occurrence of Adverse Drug Reactions/Infections by Patient Background and Treatment Factor (Overall Pediatric Patients) (Safety Analysis Set)

Patient background item Levels	Number of patients	Number of patients with adverse drug reactions	Incidence %
Race			
Asian	40	2	5.00
White	0	0	-
Black	0	0	-
Other	0	0	-
Serious bleeding			
No	36	2	5.56
Yes	4	0	0.00
Unknown	0	0	-
Surgical history			
No	32	2	6.25
Yes	7	0	0.00
Unknown	1	0	0.00
Past history			
No	36	2	5.56
Yes	4	0	0.00
Unknown	0	0	-
Breakdown of past history (overlapping tabulation)			
Hepatitis C	0	0	-
Hepatitis B	0	0	-
Other	4	0	0.00
Complications			
No	37	1	2.70
Yes	2	0	0.00
Unknown	1	1	100.00
Breakdown of complications (overlapping tabulation)			
HIV infection	0	0	-
Hypertension	0	0	-
Hyperlipidemia	0	0	-
Diabetes mellitus	0	0	-
Gastric ulcer	0	0	-
Chronic gastritis	0	0	-
Anemia	1	0	0.00

Table 1.i Occurrence of Adverse Drug Reactions/Infections by Patient Background and Treatment Factor (Overall Pediatric Patients) (Safety Analysis Set)

Patient background item Levels	Number of patients	Number of patients with adverse drug reactions	Incidence %
Epilepsy	0	0	-
Depression	0	0	-
Insomnia	0	0	-
Other	1	0	0.00
Hemophilic arthropathy			
No	38	1	2.63
Yes	1	0	0.00
Unknown	1	1	100.00
Target joint			
No	38	1	2.63
Yes	1	0	0.00
Unknown	1	1	100.00
Hepatic impairment			
No	40	2	5.00
Yes	0	0	-
Unknown	0	0	-
Breakdown of hepatic impairment (overlapping tabulation)			
Hepatitis C	0	0	-
Hepatitis B	0	0	-
Cirrhosis	0	0	-
Fatty liver	0	0	-
Other	0	0	-
Renal impairment			
No	40	2	5.00
Yes	0	0	-
Unknown	0	0	-
Breakdown of renal impairment (overlapping tabulation)			
Diabetic nephropathy	0	0	-
Renal calculus	0	0	-
Other	0	0	-

Table 1.i Occurrence of Adverse Drug Reactions/Infections by Patient Background and Treatment Factor (Overall Pediatric Patients) (Safety Analysis Set)

Patient background item Levels	Number of patients	Number of patients with adverse drug reactions	Incidence %
Allergy			
No	37	2	5.41
Yes	3	0	0.00
Unknown	0	0	-
Breakdown of allergy (overlapping tabulation)			
Drug	0	0	-
Food	2	0	0.00
Pollen	0	0	-
Other	1	0	0.00
Cause of hemophilia A			
Congenital	40	2	5.00
Acquired	0	0	-
Age at hemophilia A diagnosis (years)			
<1	23	0	0.00
≥1 and <12	15	2	13.33
≥12 and <18	1	0	0.00
≥18 and <65	0	0	-
≥65	0	0	-
Unknown	1	0	0.00
Most recent annualized bleeding rate (times/year)			
≥0 and <1	12	0	0.00
≥1 and <10	14	0	0.00
≥10	2	0	0.00
Unknown	12	2	16.67
Severity of hemophilia A (plasma residual factor VIII activity)			
Severe (<1%)	34	2	5.88
Moderate (≥1% to <5%)	5	0	0.00
Mild (≥5%)	0	0	-
Unknown (measured value unknown or not measured)	1	0	0.00

Table 1.i Occurrence of Adverse Drug Reactions/Infections by Patient Background and Treatment Factor (Overall Pediatric Patients) (Safety Analysis Set)

Patient background item Levels	Number of patients	Number of patients with adverse drug reactions	Incidence %
Status of administration of factor VIII products before the start of administration of Adynovate (most recent)			
Kovaltry	1	0	0.00
Eloctate	1	0	0.00
NovoEight	0	0	-
Advate	33	0	0.00
Kogenate FS	0	0	-
Cross eight M/MC	0	0	-
Confact F	0	0	-
Other	0	0	-
Not performed	5	2	40.00
Dosing regimen before the start of administration of Adynovate (most recent)			
Prophylaxis therapy	24	0	0.00
On-demand replacement therapy	1	0	0.00
Prophylaxis and on-demand replacement therapy	9	0	0.00
Other	1	0	0.00
Not performed	5	2	40.00
History of factor VIII inhibitor development			
No	31	2	6.45
Yes	5	0	0.00
Unknown	4	0	0.00
Family history of hemophilia			
No	24	2	8.33
Yes	13	0	0.00
Unknown	3	0	0.00
Family history of inhibitor development			
No	32	2	6.25
Yes	2	0	0.00
Unknown	6	0	0.00
Pregnancy			
No	0	0	-
Yes	0	0	-

Table 1.i Occurrence of Adverse Drug Reactions/Infections by Patient Background and Treatment Factor (Overall Pediatric Patients) (Safety Analysis Set)

Patient background item Levels	Number of patients	Number of patients with adverse drug reactions	Incidence %
Concomitant drugs			
No	33	0	0.00
Yes	7	2	28.57
Concomitant therapies			
No	40	2	5.00
Yes	0	0	-
Details of treatment			
Prophylaxis therapy	38	2	5.26
On-demand replacement therapy	0	0	-
Prophylaxis and on-demand replacement therapies*	2	0	0.00

N: number of patients included in safety evaluation; PTP: previously treated patient; PUP: previously untreated patient.

*Patients whose therapy was changed during the observation period.

Incidence %: Number of patients with adverse drug reactions / Number of patients by level * 100.

ABR in Prophylaxis Therapy

Of the 39 pediatric patients included in the efficacy evaluation of prophylaxis therapy, 38 patients (97.44%) received long-term prophylaxis therapy (11 patients [91.67%] aged <6 years, 22 patients [100.00%] aged 6 to <12 years, and 5 patients [100.00%] aged 12 to <18 years). Spontaneous bleeding occurred in 6 pediatric patients (15.79%; 2 patients [18.18%] aged <6 years and 4 patients [18.18%] aged 6 to <12 years). No patients aged 12 to <18 years who received long-term prophylaxis therapy had spontaneous bleeding (Table 1.j). The median ABR for spontaneous bleeding for pediatric patients who received long-term prophylaxis therapy was 1.53 times/year (range, 1.0 to 3.9) (1.51 times/year for patients aged <6 years and 2.00 times/year for patients aged 6 to <12 years) (Table 1.j).

Breakthrough bleeding occurred in 11 pediatric patients (28.95%) who received long-term prophylaxis therapy (4 patients [36.36%] aged <6 years, 6 patients [27.27%] aged 6 to <12 years, and 1 patient [20.00%] aged 12 to <18 years) (Table 1.k). The median ABR for breakthrough bleeding for pediatric patients who received long-term prophylaxis therapy was 2.91 times/year (range, 0.9 to 8.9) (2.46 times/year for patients aged <6 years, 2.50 times/year for patients aged 6 to <12 years, and 7.98 times/year for patients aged 12 to <18 years) (Table 1.k).

Table 1.j Annualized Bleeding Rate (Spontaneous Bleeding) (Long-Term Prophylaxis Therapy) (Effectiveness Analysis Set)

	Overall (Pediatric patients)		<6 years		6-<12 years		12-<18 years	
Prophylaxis therapy	**Number of patients/ statistics**	**%**	**Number of patients/ statistics**	**%**	**Number of patients/ statistics**	**%**	**Number of patients/ statistics**	**%**
Number of patients included in efficacy evaluation	39		12		22		5	
Number of patients receiving long-term prophylaxis therapy	38*	97.44	11*	91.67	22	100.00	5	100.00
Number of patients with spontaneous bleeding during prophylaxis therapy	6	15.79	2	18.18	4	18.18	0	0.00
Annualized bleeding rate								
Mean	1.98		1.51		2.22		-	
Standard deviation	1.21		0.72		1.43		-	
Minimum	1.0		1.0		1.0		-	
First quartile	1.00		1.00		1.02		-	
Median	1.53		1.51		2.00		-	
Third quartile	2.96		2.01		3.41		-	
Maximum	3.9		2.0		3.9		-	

Annualized bleeding rate = (number of spontaneous bleeding events during each treatment period/each treatment period) × 365.2425

*In 1 patient, the details of "prophylaxis treatment" was "immune tolerance therapy" and "perioperative administration"; therefore, this patient was excluded from tabulation.

Table 1.k Annualized Bleeding Rate (Breakthrough Bleeding) (Long-Term Prophylaxis Therapy) (Effectiveness Analysis Set)

	Overall (Pediatric patients)		< 6 years		6-12years		12-18years	
Prophylaxis therapy	Number of patients/ statistics	%	Number of patients/ statistics	%	Number of patients/ statistics	%	Number of patients/ statistics	%
Number of patients included in efficacy evaluation	39		12		22		5	
Number of patients receiving long-term prophylaxis therapy	38*	97.44	11*	91.67	22	100.00	5	100.00
Number of patients with spontaneous bleeding during prophylaxis therapy	11	28.95	4	36.36	6	27.27	1	20.00
Annualized bleeding rate								
Mean	3.68		2.23		3.94		7.98	
Standard deviation	3.01		0.93		3.49		-	
Minimum	0.9		1.0		0.9		8.0	
First quartile	1.05		1.51		1.05		7.98	
Median	2.91		2.46		2.50		7.98	
Third quartile	7.73		2.96		7.73		7.98	
Maximum	8.9		3.0		8.9		8.0	

Annualized bleeding rate = (number of spontaneous bleeding events during each treatment period/each treatment period) × 365.2425

*In 1 patient, the details of "prophylaxis treatment" was "immune tolerance therapy" and "perioperative administration"; therefore, this patient was excluded from tabulation.

Hemostatic Effectiveness of Treatment of Breakthrough Bleeding During Prophylaxis Therapy

A total of 41 breakthrough bleeding events occurred in 13 of the 40 pediatric patients (32.50%) who received prophylaxis therapy, including 6 patients (46.15%) aged <6 years, 6 patients (27.27%) aged 6 to <12 years, and 1 patient (20.00%) aged 12 to <18 years; 24 breakthrough bleeding events in 12 pediatric patients were treated with Adynovate. Treatment was rated as "excellent" for 15 of these events (62.50%), "good" for 7 events (29.17%), and "poor" for 2 events (8.33%). There was no evaluation as "fair." The 2 breakthrough bleeding events assessed as "poor" occurred in patients who had FVIII inhibition as a serious adverse drug reaction (see Section 10.3.7 of the study report); therefore, the events were considered to be associated with the impact of inhibitor development.

Table 1.l Hemostatic Effectiveness of Treatment of Breakthrough Bleeding (Effectiveness Analysis Set)

	Overall (Pediatric patients)		<6 years		6-<12 years		12-<18 years	
Treatment of breakthrough bleeding by the administration of Adynovate	**Number of patients/ events**	**%**	**Number of patients/ events**	**%**	**Number of patients/ events**	**%**	**Number of patients/ events**	**Percent age (%)**
Number of patients included in efficacy evaluation	40		13		22		5	
Number of patients receiving prophylaxis therapy	40	100.00	13	100.00	22	100.00	5	100.00
Number of patients with breakthrough bleeding during prophylaxis therapy	13	32.50	6	46.15	6	27.27	1	20.00
Number of breakthrough bleeding events	41		13		20		8	
Number of patients treated for breakthrough bleeding with Adynovate	12	92.31	6	100.00	6	100.00	0	0.00
Number of breakthrough bleeding events treated with Adynovate	24		11		13		0	
Efficacy evaluation*:								
Excellent	15	62.50	5	45.45	10	76.92	0	-
Good	7	29.17	4	36.36	3	23.08	0	-
Fair	0	0.00	0	0.00	0	0.00	0	-
Poor	2	8.33	2	18.18	0	0.00	0	-

*For evaluation, the number of events was counted instead of the number of patients.

The most common number of doses required to treat breakthrough bleeding in pediatric patients was 1, regardless of the site, severity, or type of bleeding (Table 1.m).

Table 1.m Number of Doses Required to Treat Breakthrough Bleeding and Percentage (Effectiveness Analysis Set)

		Number of doses							
	Item	1		2		3		≥4	
Breakdown of bleeding									
Bleeding site	Intraarticular	7	(100.0)	0	(0.0)	0	(0.0)	0	(0.0)
	Intramuscular	4	(80.0)	0	(0.0)	1	(20.0)	0	(0.0)
	Other	10	(83.3)	0	(0.0)	2	(16.7)	0	(0.0)
Severity of bleeding	Mild	18	(100.0)	0	(0.0)	0	(0.0)	0	(0.0)
	Moderate	3	(50.0)	0	(0.0)	3	(50.0)	0	(0.0)
	Severe	0	-	0	-	0	-	0	-
Type of bleeding	Spontaneous bleeding	11	(100.0)	0	(0.0)	0	(0.0)	0	(0.0)
	Traumatic bleeding	10	(76.9)	0	(0.0)	3	(23.1)	0	(0.0)

Hemostatic effectiveness of on-demand replacement therapy

In 2 pediatric patients (5.00%) who received on-demand replacement therapy, 2 bleeding events were treated; bleeding sites were intramuscular and other. The treatment was rated as "excellent" for both events (100.00%) (Table 1.n). Adynovate was administered 1 time for the treatment of the intramuscular event (severity, mild) and at least 4 times for the treatment of the other event (severity, mild). Both events were traumatic bleeding (Table 1.o).

Table 1.n Hemostatic effectiveness of on-demand replacement therapy (Effectiveness Analysis Set)

	Overall (Pediatric patients)		<6 years		6-<12 years		12-<18 years	
On-demand replacement therapy	**Number of patients/ events**	**%**	**Number of patients/ events**	**%**	**Number of patients/ events**	**%**	**Number of patients/ events**	**%**
Number of patients included in efficacy evaluation	40		13		22		5	
Number of patients receiving on-demand replacement therapy	2	5.00	1	7.69	1	4.55	0	0.00
Number of bleeding events	2		1		1		0	
Efficacy evaluation*:								
Excellent	2	100.00	1	100.00	1	100.00	0	-
Good	0	0.00	0	0.00	0	0.00	0	-
Fair	0	0.00	0	0.00	0	0.00	0	-
Poor	0	0.00	0	0.00	0	0.00	0	-

*For evaluation, the number of events was counted instead of the number of patients.

Table 1.o Number of Doses Required to Treat Bleeding and Percentage (Effectiveness Analysis Set)

		Number of doses							
	Item	**1**		**2**		**3**		**≥4**	
Breakdown of bleeding									
Bleeding site	Intraarticular	0	-	0	-	0	-	0	-
	Intramuscular	1	(100.0)	0	(0.0)	0	(0.0)	0	(0.0)
	Other	0	(0.0)	0	(0.0)	0	(0.0)	1	(100.0)
Severity of bleeding	Mild	1	(50.0)	0	(0.0)	0	(0.0)	1	(50.0)
	Moderate	0	-	0	-	0	-	0	-
	Severe	0	-	0	-	0	-	0	-
Type of bleeding	Spontaneous bleeding	0	-	0	-	0	-	0	-
	Traumatic bleeding	1	(50.0)	0	(0.0)	0	(0.0)	1	(50.0)

Assessor's comment:

The Applicant provided the requested separate analyses for the paediatric study population.

The paediatric population comprised overall 40 patients, 13 of whom <6 years of age, 22 aged 6 to <12, and 5 adolescent patients aged 12 to <18. 33/40 (82.5%) were PTPs according to the PTP definition used in the study (≥4 exposure days). With responses, the Applicant clarified that the majority of patients were PTPs also according to the PTP definition commonly used in the EU (≥150 EDs; 28/40). As expected from a paediatric HA population, the frequencies for haemophilic arthropathy and target joints were low (1 patient each). The majority of patients had a severe disease phenotype (34/40, 85.0%) and received Advate before the start of Adynovate administration (33/40, 82.5%).

The mean duration of routine prophylaxis with Adynovate was approximately 1 year in the overall paediatric population.

The 2 reported bleeding events reported were both traumatic bleeds of mild severity.

In total, 2 ADRs (FVIII inhibition) were reported, both from previously untreated patients. One of the events was considered a SAE.

Mean ABRs for spontaneous bleeds and breakthrough bleeds in the overall paediatric population who received long-term prophylaxis with Adynovate were 1.98 (SD 1.21) and 3.68 (SD 3.01), respectively. Patient numbers in the analysis subgroups according to paediatric age groups were too low to allow drawing of conclusions from efficacy analyses according to age groups.

In conclusion, the newly provided information from the paediatric study population do not raise concerns. No new safety signals were detected.

The issue is considered resolved.

5. CHMP overall conclusion and recommendation

☒ Fulfilled:

No regulatory action required.