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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/P46/016

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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Status of this report and steps taken for the assessment				
Current step	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Start of procedure	22/07/2024	22/07/2024	☐
☐	CHMP Rapporteur Assessment Report	26/08/2024	26/08/2024	☐
☐	CHMP members comments	09/09/2024	09/09/2024	☐
☐	Updated CHMP Rapporteur Assessment Report	12/09/2024	12/09/2024	☐
☐	CHMP adoption of conclusions:	19/09/2024	19/09/2024	☐
☐	Submission	15/10/2024	15/10/2024	☐
☐	Re-start	16/10/2024	16/10/2024	☐
☐	CHMP Rapporteur Assessment Report	30/10/2024	30/10/2024	☐
☐	CHMP members comments	04/11/2024	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	07/11/2024	n/a	☐
☒	CHMP adoption of conclusions:	14/11/2024	14/11/2024	☐

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1. Introduction

On 20 June 2024, the MAH submitted a completed paediatric study (study 261603) 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 261603 is a stand-alone study.

The study is not part of the PIP or the clinical development program of Adynovi. It is a post-marketing surveillance (PMS) study, which was conducted in South Korea to investigate the safety and hemostatic effectiveness of ADYNOVATE in routine clinical practice. This study was required by Korea's Ministry of Food and Drug Safety (MFDS) according to 'Standards for Re-examination of New Drugs' to assess the safety and describe hemostatic effectiveness for the approved local label of ADYNOVATE in a real-world setting in South Korea.

The Company declares that the study results do not require an update to the Product Information of Adynovi.

2.2. Information on the pharmaceutical formulation used in the study

Rurioctocog alfa pegol (ADYNOVATE) is a PEGylated full-length recombinant human FVIII with an extended half-life (EHL). It belongs to the pharmacotherapeutic group of coagulation FVIII (ATC code: B02BD02).

Rurioctocog alfa pegol was first authorized in the United States on 13 Nov 2015 (under the trade name ADYNOVATE); it is indicated for on-demand treatment and control of bleeding, routine prophylaxis, and perioperative management in children and adults with hemophilia A. In the EU, rurioctocog alfa pegol (under the trade name Adynovi) was authorized on 08 Jan 2018; it is indicated for treatment and prophylaxis of bleeding in patients 12 years and above with hemophilia A (congenital FVIII deficiency).

As of 31 Dec 2023, rurioctocog alfa pegol was licensed in 64 countries worldwide under the tradenames ADYNOVATE or Adynovi.

Adynovi is a powder and solvent for solution for injection.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- **Study 261603**, a multicenter, prospective, noninterventional PMS study with no mandated treatments per ADYNOVATE prescribing information, visits, or assessments. The study also included patients aged <18 years; 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).

2.3.2. Clinical study

Study 261603

Description

Study 261603 was a multicenter, prospective, noninterventional PMS study with no mandated treatments per ADYNOVATE prescribing information, visits, or assessments. The study aimed to collect patient- and treatment-related data of at least 330 patients on ADYNOVATE therapy over a 6-year period required by the MFDS.

Based on the requirement by MFDS, this study was conducted for 6 years (31 January 2018 ~ 30 January 2024) to characterize the safety and describe hemostatic effectiveness of ADYNOVATE under standard clinical care in South Korea. In this study, physicians are collecting the data of safety and effectiveness at 0 month (baseline), 1 month, 6 months, and at unscheduled visits which may occur during routine care.

Methods

Study participants

Inclusion criteria:

Patients with a diagnosis of hemophilia A who were newly prescribed with ADYNOVATE or who already have been prescribed ADYNOVATE according to the physician's judgment shall be included in this study if:

1. The patient or legally authorized representative has given written informed consent to participate in the study.

2. The patient is indicated for treatment according to the ADYNOVATE South Korea prescribing information (PI).

Exclusion Criteria:

1. The patient or legally authorized representative does not wish to participate in the study.

2. Any of the contraindications included in the PI for ADYNOVATE apply.

3. Patient is enrolled in an interventional trial using an investigational product other than ADYNOVATE

Assessor`s comment:

One inclusion criterion of this study was when the patient is indicated for treatment according to the ADYNOVATE South Korea prescribing information (PI). No comparison was provided between the South Korean PI and the European PI. For example, are the indications for use the same between South Korea and the European Union, as well as the target population, posology and method of administration?

The applicant was asked to provide a statement pertaining to potential differences between the labels. If discrepancies are identified between the South Korean and EU product (information), (especially related to the indication, target population, posology of administration) the Applicant was asked to discuss them with regard to this study and comment on applicability of study results for the EU**.** The

Applicant`s review of the EU Summary of Product Characteristics (SmPC) and the South Korean package insert (PI) for ADYNOVATE reveals no major differences, aside from the indicated patient age groups. The South Korean PI includes children, adolescents, and adults with hemophilia A, whereas the EU SmPC specifies patients aged 12 years and above. Stylistic differences, such as the wording for dosing schedules are considered negligible. As the South Korean treatment recommendations are basically similar to the EU recommendations, the study 261603 results are applicable also to the EU population.

Treatments

This is a non-interventional study based on secondary use of data collected for other purposes. No administration of any therapeutic or prophylactic agent is required in this protocol, and there are no procedures required as part of this protocol.

There was a so called "observation period". The observation period documented at least 3 data collection points (Baseline, 1 month and 6 months). According to the applicant given the knowledge of the pharmacokinetics and safety profile of ADYNOVATE, hemostatic effectiveness and safety issues can be assessed during the 6-month observation period.

Objective(s)

The purpose of this study is to characterize the safety and describe hemostatic effectiveness in patients receiving ADYNOVATE in routine clinical practice.

The primary objective was to characterize the safety of ADYNOVATE when used in standard clinical practice of hemophilia A patients in South Korea. The secondary objectives were to monitor long term safety of ADYNOVATE in pediatric and adult patients with hemophilia A and to evaluate hemostatic effectiveness in patients with hemophilia A receiving ADYNOVATE under standard clinical care in South Korea.

Outcomes/endpoints

The safety evaluation was conducted using safety data collected on the following occurring coincident with use of ADYNOVATE:

• The incidence of all types of AEs for the SFAS overall and by subgroup

• The incidence and frequency of AEs, further classified by serious, severity, and reported causal relationship to ADYNOVATE

• All AEs that occurred during or after first ADYNOVATE administration (categorization according to the MedDRA). All AEs were summarized by SOC and PT, and were cross-tabulated for relatedness, seriousness, and severity

• Inhibitor titers for FVIII antibodies by incidence and by high and lower titer categories

• Occurrence of AE by demographics and baseline characteristics

• Abnormal laboratory results

Furthermore a multivariate logistic regression model was performed to determine whether renal, hepatic, or neurological disorder (RHN) AEs are significantly more probable for any of the age groups (infants & toddlers, children, adolescents, adults, or elderly age groups), cumulative ADYNOVATE exposure in IU/kg, and presence of renal, hepatic, or neurological disorders at baseline. This analysis was examined to determine whether RHN AEs are significantly more probable for interactions of the above factors, if there are sufficient degrees of freedom to allow these comparisons.

The effectiveness evaluation was included as follows:

Effectiveness assessment was analyzed each regimen for treatment with ADYNOVATE overall and by subgroup. Additionally, effectiveness assessment was analyzed by age categories (<2 years, ≥ 2 ~ <12 years, ≥ 12 ~ < 18 years, ≥ 18 years).

• The total number (%) of treated bleeds and their corresponding hemostatic effectiveness ratings using the 4-point Likert scale as assessed by the patients/caregiver for treatments given at home, or by the physician for treatments given in the hospital/clinic

• Effectiveness assessment for on-demand treatment with ADYNOVATE and control of bleeding episodes

• Effectiveness assessment for routine prophylaxis treatment with ADYNOVATE. This regimen was performed in two treatment periods as follows:

- on-study treatment period for prophylaxis-only exposure: Treatment period for the purpose of prophylaxis in 'Prophylaxis/Perioperative Therapy' page in eCRF

- on-study treatment period for prophylaxis and bleed-treatment exposure: The sum of treatment period for the purpose of prophylaxis in the 'Prophylaxis/Perioperative Therapy' page and the treatment period in the 'Administration for bleeding during Prophylaxis' page in eCRF. Overlapping periods were not double-counted.

• Assessment of perioperative effectiveness of ADYNOVATE

Assessment of effectiveness

1. Bleeding Assessment

Each individual bleed, spontaneous or traumatic, will be recorded in patient's diary, and/or recorded in study physician/nurse/clinic notes.

2. Number of ADYNOVATE infusions needed for the treatment of bleeding episodes

The number of ADYNOVATE infusions needed for each bleeding episode is determined by the patient, his/her caregiver, and/or clinician treating the patient, and is based upon the patient's response to treatment, using the Efficacy Rating Scale for Treatment of Bleeding Episodes in Table 5. An infusion is defined as completion of administration of the calculated dose of ADYNOVATE. If an infusion is interrupted, e.g., due to vascular access issues, and must be re-started, it will be recorded as 1 infusion. If an infusion is terminated for any reason prior to completion of infusion and not restarted, it will be recorded as an infusion; reasons for not completing the infusion will be recorded.

3. Overall hemostatic effectiveness rating at resolution of bleed

For each bleeding episode, the following information will be recorded by the patient (via their caregiver) or by authorized, qualified personnel at the participating site:

• Type of bleed, e.g., spontaneous (definitely no injury/trauma), injury (definitely due to injury/trauma), or unknown (pediatric patient was not observed by an adult to reliably determine and verify whether it was spontaneous or injury-related).

• Date and time of onset of bleed

• Date and time of each infusion of ADYNOVATE required achieving adequate hemostasis.

• Date and time of resolution of bleeding episode

• Overall clinical efficacy rating according to the rating scale as described in Table 5 at resolution of bleed.

The patient or their caregiver rated the overall treatment response at resolution of bleed. Total number (%) of treated bleeds and their corresponding hemostatic effectiveness ratings using an "excellent-to-none" 4-point Likert scale by the patient/caregiver (patient <12 years: care-giver, patient ≥ 12 years: self-assessment) for treatments given at home, or by the study physician for treatments given in the hospital/clinic (table 5).

Study physician rated effectiveness ("none", "fair", "good", or "excellent") by bleed severity.

Table 1: Effectiveness rating scale for treatment of bleeding episodes

Excellent	Full relief of pain and cessation of objective signs of bleeding (eg, swelling, tenderness, and decreased range of motion in the case of musculoskeletal 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.
None [i]	No improvement of signs or symptoms or conditions worsen.

Table 2: Peri-operative effectiveness assessment scale

Rating	Criteria	Score
Excellent	Perioperative blood loss was less than or equal to (≤ 100%) that expected for the type of procedure performed in a non-hemophilic population, Required blood components for transfusions were less than or similar to that expected in non-hemophilic population	3
Good	Perioperative blood loss was up to 50% more (101% to 150%) than expected for the type of procedure performed in a non-hemophilic population Required blood components for transfusions were less than or similar to that expected in non-hemophilic population	2
Fair	Perioperative blood loss was more than 50% of that expected for the type of procedure performed in a non-hemophilic population (> 150%) Required blood components transfusions were greater than that expected in non-hemophilic population	1
None	Significant perioperative bleeding that was the result of inadequate therapeutic response despite proper dosing, necessitating rescue therapy Required blood components for transfusions were substantially greater than that expected in non-hemophilic population	0

Patient Diary

It is considered standard practice for patients with haemophilia to maintain a diary which captures treatments and disease-related data.

Diaries were offered to each patient or their caregivers at baseline visit to record the following information:

• Details of bleeding episodes and response to treatment

• Number of ADYNOVATE units required for bleed resolution

• Number of ADYNOVATE infusions required for bleed resolution

• Untoward events

• Effectiveness rating according to the rating scale as described in Table 5 above for the treatment of bleeding episodes

Completion of the patient diary was a voluntary effort by the individual patient or patient´s legally authorized representative. Patient entries in the diary was served as source records. If used, the diary remained with the patient for the duration of the study. Untoward events recorded in the diary are reported as AEs according to the study physician's discretion and clinical judgment.

Assessor`s comment:

The definition of "bleed/bleeding" is unclear. Since there were 9 institutes included in the PMS study and also self-reporting was used, a general definition of "bleed/bleeding" should have been given in advance for the sake of consistency and to allow a general assessment of the bleeding events. This shortcoming hampers any efficacy conclusions based on study results. However, in light of the procedure and the overall limited impact of this study on the B/R balance of Adynovi, no question is raised.

Sample size

The prevalence of hemophilia A, varying from moderate to severe, is reported to range from 0.4 to 20.7 cases per 100,000 males in different regions of the world. In South Korea, the prevalence for hemophilia A (all severities) was 5.3 per 100,000. According to the Korean Hemophilia Foundation (KHF) 2019 annual report, the number of patients with hemophilia A in South Korea in 2019 was 1,746 and considering the average annual number of newly diagnosed patients, 1,856 patients were expected in 2023.

In South Korea, 82% of FVIII used is recombinant FVIII. Comparing the recombinant FVIII total IUs in WFH 2021 with the domestic sales data, it was estimated that 366 patients (24%) are treated with ADYNOVATE. Considering the limitations (site decline, patient or their guardian refuse to participate in PMS study, etc.), Takeda estimates that the total number of patients in this study was at least 330.

Assessor's comment

Study 261603 did not include hypothesis testing and no formal sample size calculation was provided. The study was a post-marketing surveillance study. According to the protocol, the target enrollment was at least 330 patients.

Randomisation and blinding (masking)

Not applicable. This was a non-interventional study.

Statistical Methods

All analyses were descriptive and included specifically but not exclusively, arithmetic means, medians, standard deviations, minimum, maximum, 25th and 75th percentiles for continuous variables; frequency counts, proportions for categorical variables; and 95% confidence intervals around select point estimates.

The number of patients included in each analysis set was reported.

Analyses were be performed using available data. Due to the non-interventional nature of the study, missing values were expected. No imputations were made for missing values. The following variables have been included in the descriptive analysis: age, gender, comorbid conditions, and pertinent medical history.

Assessor's comment

The study did not include hypothesis testing. The results were summarized descriptively using mean (SD), 95% CI, median (min; max) for continuous variables, and 'N' and proportion (%) for categorical variables. This seems appropriate for that kind of study and the objectives evaluated.

Results

Participant flow

A total of 339 patients' eCRFs were retrieved. Of these 339 patients, 309 patients completed the study; 30 patients withdrew from the study due to various reasons: 'Adverse Event' (1 patient), 'Voluntary Withdrawal' (2 patients), 'Physician Decision' (6 patients), 'Lost to Follow-up' (17 patients), and 'Other' (4 patients). Completed patients represent patients who completed their scheduled visits, and their data was entered in electronic data capture (EDC). 1 patient withdrew from the study on the day of enrollment but then re-enrolled two years later as a new patient and completed the study (this patient was counted only once).

Table 3: patient disposition

	All patients (N=339)	Patients newly prescribed with ADYNOVATE[a] (N=29)	Patients previously treated with ADYNOVATE[b] (N=310)
Enrolled/Signed informed consent	339	29	310
Completed	309	23	286
Withdrawals	30	6	24
Adverse Event	1	0	1
Voluntary Withdrawal	2	1	1
Physician Decision	6	2	4
Lost to Follow-up	17	2	15
Other	4	1	3

a: Patients newly prescribed with ADYNOVATE: If product of FVIII treatment history and FVIII product used at the time of inhibitor detection are both not 'ADYNOVATE'

b: Patients previously treated with ADYNOVATE: If product of FVIII treatment history or FVIII product used at the time of inhibitor detection is 'ADYNOVATE'

Patient withdrew from the study on the day of enrollment, but then re-enrolled two years later as patient and completed the study. This patient is counted only once in this table.

Assessor`s comment:

Percentages are missing in this table.

Comparing the % of withdrawals roughly, it is obvious that rates are considerably higher for the newly prescribed patients. This is not surprising because patients who can't 'tolerate' the drug stop early, therefore such patients would already be "gone/lost" in the previously treated group. No concerns are raised.

Recruitment

Electronic Case Report Forms (eCRFs) were collected from 9 institutions in South Korea. Information regarding patient demographics, medical history, haemophilia A history, history of inhibitor development, FVIII treatment history, vital signs, treatment status, and other assessments (clinical and other data and safety) was collected at baseline visit. Additional information regarding abnormal laboratory test, vital signs, ADYNOVATE clotting assay, inhibitor development to ADYNOVATE, treatment status, and other assessments (clinical and other data and safety) was collected at follow up visits.

The study period included the time between 31 January 2018 and 30 January 2024.

Assessor`s comment

The study period was 6 years (31 January 2018 - 30 January 2024). Study duration was 6 months. Each patient had baseline, 1 month and 6 months visits. In how far this duration is sufficient to capture long-term safety is not further commented on, but it seems rather short compared to regulatory standard in the EU.

Baseline data

A summary of baseline demographics for all randomized subjects is presented in Table 9. Overall, 338 subjects were enrolled (336 males [99,41%] and 2 females [0,59%]. The mean (± SD) age at baseline was 24.98 ± 13.21 years, ranged from minimum of 1.00 year to maximum of 61.00 years.

The distribution by age group showed that adults (≥18 ~ <65 years) accounted for 72.19% (244/338 patients), followed by children (≥2 ~ <12 years) for 15.38% (52/338 patients), adolescents (≥12 ~ <18 years) for 11.83% (40/338 patients), infants & toddlers (<2 years) for 0.59% 2/338 patients), and none of the elderly aged more than 65 years.

Table 4: Demographic and baseline characteristics

	All patients (N=338)	Patients newly prescribed with ADYNOVATE[a] (N=29)	Patients previously treated with ADYNOVATE[b] (N=309)
Age[c] (years)			
n	338	29	309
mean (SD)	24.98 (13.21)	21.90 (13.01)	25.27 (13.22)
min	1.00	2.00	1.00
Q1 (25 percentile)	15.00	12.00	16.00
median	24.00	24.00	24.00
Q3 (75 percentile)	33.00	27.00	33.00
max	61.00	49.00	61.00
Age groups[c], n (%)			
Infants & toddlers (<2 years)	2 (0.59)	0 (0.00)	2 (0.65)
Children (≥2 ~ <12 years)	52 (15.38)	5 (17.24)	47 (15.21)
Adolescents (≥12 ~ <18 years)	40 (11.83)	6 (20.69)	34 (11.00)
Adults (≥18 ~ <65 years)	244 (72.19)	18 (62.07)	226 (73.14)
Elderly (≥65 years)	0 (0.00)	0 (0.00)	0 (0.00)
Total	338	29	309
Age intervals[c] (years, category), n (%)			
< 10	45 (13.31)	5 (17.24)	40 (12.94)
10 ~ < 20	73 (21.60)	6 (20.69)	67 (21.68)
20 ~ < 30	111 (32.84)	12 (41.38)	99 (32.04)
30 ~ < 40	59 (17.46)	3 (10.34)	56 (18.12)
40 ~ < 50	34 (10.06)	3 (10.34)	31 (10.03)
≥ 50	16 (4.73)	0 (0.00)	16 (5.18)
Total	338	29	309
Gender, n (%)			
Male	336 (99.41)	29 (100.00)	307 (99.35)
Female	2 (0.59)	0 (0.00)	2 (0.65)
Total	338	29	309
Height (cm)			
n	233	23	210
missing	105	6	99
mean (SD)	165.10 (19.05)	155.74 (27.95)	166.12 (17.61)
min	91.00	91.00	97.10
Q1 (25 percentile)	164.80	154.20	165.90
median	170.40	169.30	170.85
Q3 (75 percentile)	175.00	174.00	175.00
max	191.20	179.60	191.20
Weight (kg)			

	All patients (N=338)	Patients newly prescribed with ADYNOVATE[a] (N=29)	Patients previously treated with ADYNOVATE[b] (N=309)
n	276	28	248
missing	62	1	61
mean (SD)	65.38 (23.06)	59.20 (26.71)	66.08 (22.57)
Min	10.00	11.70	10.00
Q1 (25 percentile)	57.00	45.50	57.80
median	70.00	64.00	70.00
Q3 (75 percentile)	79.00	74.50	79.40
max	129.00	118.00	129.00
Systolic Blood Pressure (mmHg)			
n	36	8	28
missing	302	21	281
mean (SD)	113.14 (11.30)	113.50 (8.38)	113.04 (12.14)
min	90.00	97.00	90.00
Q1 (25 percentile)	110.00	110.00	109.50
median	110.00	115.00	110.00
Q3 (75 percentile)	120.00	120.00	119.50
max	146.00	121.00	146.00
Diastolic Blood Pressure (mmHg)			
n	36	8	28
missing	302	21	281
mean (SD)	72.61 (9.81)	71.38 (8.26)	72.96 (10.32)
min	55.00	58.00	55.00
Q1 (25 percentile)	70.00	66.50	70.00
median	70.00	70.00	70.00
Q3 (75 percentile)	80.00	80.00	80.00
max	100.00	80.00	100.00
Heart Rate (beats/min)			
n	37	8	29
missing	301	21	280
mean (SD)	82.41 (15.14)	78.13 (6.60)	83.59 (16.64)
min	51.00	70.00	51.00
Q1 (25 percentile)	72.00	72.00	74.00
median	80.00	78.00	82.00
Q3 (75 percentile)	88.00	83.50	95.00
max	116.00	88.00	116.00

SD = standard deviation, min = minimum, max = maximum
Denominator of percentage is the number of 'Total' except for missing data.
a: Patients newly prescribed with ADYNOVATE: if product of FVIII treatment history and FVIII product used at the time of inhibitor detection are both not 'ADYNOVATE'
b: Patients previously treated with ADYNOVATE: if product of FVIII treatment history or FVIII product used at the time of inhibitor detection is 'ADYNOVATE'
c: Age at enrollment.

Data from 312 patients was available for analysis of hemophilia A diagnosis duration. The mean (standard deviation [SD]) of hemophilia A diagnosis duration was 18.99 (9.33) years.

For 338 patients, the mean (SD) of FVIII levels at baseline was 7.33% (13.18%).

The mean (SD) of bleeding episodes per patient in the 12 months prior to the study by severity was 3.84 (8.01) for mild episodes, 0.84 (3.42) for moderate episodes, and 0.71 (7.45) for severe episodes.

History of thromboembolism was unknown for 7 patients and 331 patients did not have a history of thromboembolism.

Among 326 patients with reported data, 28 (8.59%) patients had a family history of inhibitors.

Thirteen of 338 (3.85%) patients had a history of inhibitor development and a history of inhibitor titer level.

All 338 patients had FVIII treatment history.

Table 5: Baseline FVIII levels

	Patients (N=338)
Baseline FVIII levels (%)	
n	338
mean (SD)	7.33 (13.18)
min	0.00
Q1 (25 percentile)	0.70
median	1.80
Q3 (75 percentile)	6.50
max	82.90

SD = standard deviation, min = minimum, max = maximum

Table 6: The number of bleeding episodes by severity in the 12 months prior to the study

	All patients (N=338)	Patients newly prescribed with ADYNOVATE[a] (N=29)	Patients previously treated with ADYNOVATE[a] (N=309)
All			
n	338	29	309
mean (SD)	5.40 (11.45)	7.48 (23.14)	5.20 (9.71)
min	0.00	0.00	0.00
Q1 (25 percentile)	0.00	0.00	0.00
median	2.00	1.00	2.00
Q3 (75 percentile)	6.00	4.00	6.00
max	125.00	125.00	63.00
Mild			
n	338	29	309
mean (SD)	3.84 (8.01)	3.00 (5.02)	3.92 (8.23)
min	0.00	0.00	0.00
Q1 (25 percentile)	0.00	0.00	0.00
median	1.00	1.00	1.00
Q3 (75 percentile)	4.00	4.00	4.00
max	63.00	23.00	63.00
Moderate			
n	338	29	309
mean (SD)	0.84 (3.42)	0.55 (1.59)	0.87 (3.54)
min	0.00	0.00	0.00
Q1 (25 percentile)	0.00	0.00	0.00
median	0.00	0.00	0.00
Q3 (75 percentile)	0.00	0.00	0.00
max	39.00	8.00	39.00
Severe			
n	338	29	309
mean (SD)	0.71 (7.45)	3.93 (20.98)	0.41 (4.44)
min	0.00	0.00	0.00
Q1 (25 percentile)	0.00	0.00	0.00
median	0.00	0.00	0.00
Q3 (75 percentile)	0.00	0.00	0.00
max	113.00	113.00	60.00

SD = standard deviation, min = minimum, max = maximum
If a patient did not report a bleed, it assumed that this patient had 0 bleeds.
a: Patients newly prescribed with ADYNOVATE: If product of FVIII treatment history and FVIII product used at the time of inhibitor detection are both not 'ADYNOVATE'
b: Patients previously treated with ADYNOVATE: If product of FVIII treatment history or FVIII product used at the time of inhibitor detection is 'ADYNOVATE'

Table 7: FVIII treatment history

	Patients (N=338)
FVIII treatment history, n (%)	
Yes	338 (100.00)
No	0 (0.00)
Total	338
FVIII product, n (%)	
Prophylaxis	315 (93.20)
Advate	185 (54.73)
Eloctate	0 (0.00)
Xyntha	3 (0.89)
Novoseven RT	0 (0.00)
Greengene F	9 (2.66)
Greenmono	21 (6.21)
Kogenate FS	1 (0.30)
Adynovate	286 (84.62)
Other	3 (0.89)
On-demand	162 (47.93)

A total of 26 (7.69%) patients had a past medical history, 50 (14.79%) patients had comorbid conditions, and 57 (16.86%) received concomitant medication.

Baseline data in special patients

Special patients were defined as paediatrics (children aged under 12 years and adolescent aged more than 12 years and less than 18 years), elderly (patients aged more than 65 years), pregnant or breastfeeding women, patients with renal impairment, patients with hepatic impairment, and patients for long-term use (patients who received the ADYNOVATE for 6 months (182.625 days) or more).

Among 338 patients, 15.38% (52/338 patients) were children, 11.83% (40/338 patients) were adolescents, and 0.59% (2/338 patients) were infants and toddlers.

Among 338 patients, 0.70% (2/284 patients) had pregnant partners. However, after database lock, it was discovered that one of the reports of a pregnant partner of a male patient was erroneous. There was only one male patient with a pregnant partner, not two.

Among 338 patients, 2.37% (8/338 patients) had hepatic impairment in the past, and 0.89% (3/338 patients) had hepatic impairment at enrollment.

Among 338 patients, 20.71% (70/338 patients) were patients for long-term use.

During this re-examination period, there was no elderly patient, pregnant or breastfeeding woman, and patient with renal impairment among 338 patients.

Table 8: Special patients

	Patients (N=338)
Age groups[a], n (%)	
Infants & toddlers (<2 years)	2 (0.59)
Children (≥2 ~ <12 years)	52 (15.38)
Adolescents (≥12 ~ <18 years)	40 (11.83)
Adults (≥18 ~ <65 years)	244 (72.19)
Elderly (≥65 years)	0 (0.00)
Total	338
Pregnancy, n (%)	
Yes, pregnant female patient	0 (0.00)
Yes, pregnant partner of male patient[c]	2 (0.70)
No	282 (99.30)
Total	284
Not Applicable	54
Breastfeeding women, n (%)	
Yes	0 (0.00)
No	2 (100.00)
Total	2
Not Applicable	336
Renal impairment, n (%)	
Yes, in the past (see Table 2.11 Medical history)	0 (0.00)
Yes, at enrollment (see Table 2.12 Comorbid conditions)	0 (0.00)
No	338 (100.00)
Total	338
Hepatic impairment, n (%)	
Yes, in the past (see Table 2.11 Medical history)	8 (2.37)
Yes, at enrollment (see Table 2.12 Comorbid conditions)	3 (0.89)
No	327 (96.75)
Total	338
Patients for long-term use[b], n (%)	
Short term use < 6 months (< 182.625 days)	268 (79.29)
Long term use ≥ 6 months (≥ 182.625 days)	70 (20.71)
Total	338

Denominator of percentage is the number of 'Total' except for not applicable data.
a: Age at enrollment.
b: Patients for long-term use: If On-study overall treatment period over 6 months (≥ 182.625 days)
- On-study overall treatment period = Max('Regimen treatment stop date' for the last prophylaxis/perioperative form, 'Infusion Date' for the last on-demand therapy form) - Min('Regimen treatment start date' for the first prophylaxis/perioperative form, 'Infusion Date' for the first on-demand therapy form) + 1 day
c: After database lock, it was discovered that one of the reports of a pregnant partner of a male patient was erroneous. There was only one male patient with a pregnant partner, not two.

Baseline data in pediatric patients

Pediatric Patients Aged <2 Years (N=2): The mean (SD) of hemophilia A diagnosis duration was 1.06 (0.54) years. The mean (SD) of bleeding episodes per patient in the 12 months prior to the study by severity was 2.50 (0.71) for mild episodes, 1.00 (0.00) for moderate episodes, and 0.00 (0.00) for severe episodes. No patients in this age group had family history of inhibitors, a history of inhibitor development or a history of inhibitor titer level.

Pediatric Patients Aged ≥2 to <12 Years (N=52): The mean (SD) of hemophilia A diagnosis duration was 5.63 (3.23) years. The mean (SD) of bleeding episodes per patient in the 12 months prior to the study by severity was 2.38 (3.76) for mild episodes, 0.69 (2.10) for moderate episodes, and 0.08 (0.39) for severe episodes. Six (11.76%) of the 51 patients with reported family history data had family history of inhibitors.

Six (11.54%) of the 52 patients had a history of inhibitor development or a history of inhibitor titer level.

Pediatric Patients Aged ≥12 to <18 years (N=40): The mean (SD) of hemophilia A diagnosis duration in 39 patients who had data available for analysis was 12.94 (3.27) years. The mean (SD) of bleeding episodes per patient in the 12 months prior to the study by severity was 2.58 (4.54) for mild episodes, 0.45 (1.24) for moderate episodes, and 0.03 (0.16) for severe episodes. Four (10.53%) of the 38 patients with reported family history data had family history of inhibitors. No patients in this age group had a history of inhibitor development or a history of inhibitor titer level.

Number analysed

Of the 339 patients enrolled and signed informed consent in this study, 1 patient was lost to follow-up, with no record of having ADYNOVATE treatment after informed consent, and was excluded from the SAS, the SFAS, and EFAS (Table 8)

During this re-examination period, SFAS and EFAS were used for analyses of safety and effectiveness data in this study, respectively.

Table 9: analysis sets (enrolled set)

	All patients (N=339)	Patients newly prescribed with ADYNOVATE[e] (N=29)	Patients previously treated with ADYNOVATE[f] (N=310)
Enrolled/Signed informed consent	339	29	310
Safety Analysis Set (SAS)[a]	338	29	309
Enrolled patients who are excluded from Safety Analysis Set (SAS)[a]	1	0	1
Patient was lost to follow-up with no record of having ADYNOVATE treatment prior to being lost to follow-up.	1	0	1
Off-Label Analysis Set (OLAS)[b]	0	0	0
Safety Follow-Up Analysis Set (SFAS)[c]	338	29	309
Patients in SAS who are excluded from Safety Follow-Up Analysis Set (SFAS)[c]	0	0	0
Effectiveness Full Analysis Set (EFAS)[d]	338	29	309
Patients in SFAS who are excluded from Effectiveness Full Analysis Set (EFAS)[d]	0	0	0

a: Safety Analysis Set: All patients who were enrolled and received at least 1 infusion of ADYNOVATE, and for whom the infusion followed the South Korean package insert.
b: Off-Label Analysis Set: All patients who have received at least one infusion of ADYNOVATE, and for whom the infusion did not follow the South Korean package insert.
c: Safety Follow-Up Analysis Set: As a subset of the Safety Analysis Set (SAS) and contains all patients who have at least one safety follow-up.
d: Effectiveness Full Analysis Set: The subset of patients in the Safety Follow-up Analysis Set (SFAS) who have had at least one effectiveness evaluation. This means that one of the following conditions are met:
1) The patient has completed the entire study without reporting any bleeds or,
2) The bleeding episode information or its effectiveness assessment has been filled in on at least one of the following forms: Administration for bleeding during prophylaxis, On-demand control of bleeding, or Surgical Procedures Log.
e: Patients newly prescribed with ADYNOVATE: If product of FVIII treatment history and FVIII product used at the time of inhibitor detection are both not 'ADYNOVATE'
f: Patients previously treated with ADYNOVATE: If product of FVIII treatment history or FVIII product used at the time of inhibitor detection is 'ADYNOVATE'
Patient : withdrew from the study on the day of enrollment, but then re-enrolled two years later as patient and completed the study. This patient is counted only once in this table.

Efficacy results

Overall, 314 (92.90%) patients received prophylaxis treatment, 23 (6.80%) patients received on-demand treatment, and 9 (2.66%) patients received perioperative treatment. The most frequent

treatment reasons for prophylaxis treatment were "Prophylaxis only" in 201 (59.47%) patients and " Prophylaxis and on-demand" in 107 (31.66%) patients.

Table 10: Adynovate Treatment Status

	Patients (N=338)	Prophylaxis Regimen Patients (N=314)	On-demand Regimen Patients (N=23)	Perioperative Regimen Patients (N=9)
Total dose[a] (IU)				
n	338	314	23	9
Mean (SD)	75,557.87 (44,635.54)	77,399.10 (44,743.94)	57,011.83 (35,428.35)	12,150.78 (17,459.33)
Min	514.00	514.00	4,958.00	1,270.00
Median	76,238.50	77,584.50	44,456.00	2,544.00
Max	217,545.00	217,545.00	117,828.00	52,884.00
Dosage per week[b, c] (IU/kg/wk)				
n	316	292	23	9
missing	22	22	–	–
Mean (SD)	61.63 (89.68)	61.95 (91.34)	38.66 (18.32)	235.84 (107.96)
Min	2.94	2.94	4.34	35.00
Median	55.25	56.06	37.48	235.55
Max	1,364.44	1,364.44	73.97	404.56
Total number of infusion[d] (infusions)				
n	338	314	23	9
Mean (SD)	40.29 (18.34)	41.18 (17.99)	31.22 (18.21)	7.67 (10.48)
Min	1.00	1.00	2.00	1.00
Median	45.50	46.00	32.00	4.00
Max	87.00	87.00	57.00	26.00
Total number of infusion[d] (infusions, category), n (%)				
<30	92 (27.22)	80 (25.48)	10 (43.48)	9 (100.00)
≥30 ~ <50	137 (40.53)	130 (41.40)	8 (34.78)	0 (0.00)
≥50 ~ <70	96 (28.40)	91 (28.98)	5 (21.74)	0 (0.00)
≥70	13 (3.85)	13 (4.14)	0 (0.00)	0 (0.00)
Total	338	314	23	9

	Patients (N=338)	Prophylaxis Regimen Patients (N=314)	On-demand Regimen Patients (N=23)	Perioperative Regimen Patients (N=9)
Mean dose per infusion[e] (IU/infusion)				
n	338	314	23	9
Mean (SD)	1,901.29 (654.27)	1,895.82 (661.44)	1,948.53 (525.58)	1,629.61 (783.69)
Min	250.00	250.00	533.89	636.00
Median	2,014.68	2,009.01	2,028.07	1,731.00
Max	3,634.91	3,634.91	2,661.83	3,125.00
Mean dose per infusion[e] (IU/infusion, category), n (%)				
<1,000	41 (12.13)	39 (12.42)	2 (8.70)	2 (22.22)
≥1,000 ~ <2,000	114 (33.73)	107 (34.08)	6 (26.09)	4 (44.44)
≥2,000	183 (54.14)	168 (53.50)	15 (65.22)	3 (33.33)
Total	338	314	23	9

max=maximum; min=minimum; N=number of patients; n=number of patients per criterion; SD=standard deviation; wk=week.
Denominator of percentage is the number of 'Total'.

[a] Total dose = Total dose of prophylaxis therapy + Total dose of perioperative therapy + Total dose of on-demand therapy
- Total dose of prophylaxis or perioperative therapy: Sum of total dose (Total dose='Total number of infusion' * 'Total dose per infusion (IU)') .
- Total dose of on-demand therapy: Sum of on-demand therapy for on-demand patient and on-demand therapy for prophylaxis patient.
On-demand therapy for on-demand patient=Sum of 'Total dose per infusion (IU)' for all entries on the On Demand Therapy page for this patient.
On-demand therapy for prophylaxis patient=Sum of 'Total dose (IU)' from Administration for bleeding during Prophylaxis.

[b] Dosage per week: Total dosage/(On-study treatment period/7).
i) Total dosage = Total dosage of prophylaxis therapy + Total dosage of perioperative therapy + Total dosage of on-demand therapy
- Total dosage of prophylaxis or perioperative therapy: Sum of total dosage (Total dosage='Total number of infusion' + 'Dosage per infusion (IU/kg)')
- Total dosage of on-demand therapy: Total dosage of the On-Demand therapy + Total dosage of Administration for bleeding during Prophylaxis
Total dosage of the On-Demand Therapy = Sum of 'Dosage per infusion (IU/kg)', Total dosage of Administration for bleeding during Prophylaxis = Sum of Total dosage/Body weight at baseline.
ii) On-study treatment period = Max ('Regimen treatment stop date' for the last prophylaxis/perioperative form, 'Infusion Date' for the last on-demand therapy form) Min ('Regimen treatment start date' for the first prophylaxis/perioperative form, 'Infusion Date' for the first on-demand therapy form) + 1.

[c] Dosage per week by treatment regimen.
i) Prophylaxis=Total dosage of prophylaxis/(On-study treatment period for prophylaxis/7).
On-study treatment period for prophylaxis= Max ('Regimen treatment stop date' for the last prophylaxis/perioperative page where Treatment Regimen = Prophylaxis) Min ('Regimen treatment start date' for the first prophylaxis/perioperative page.
where Treatment Regimen = Prophylaxis) + 1 day.
ii) On-demand=Total dosage of on-demand/(On-study treatment period for on-demand/7.)
On-study treatment period for on-demand= Max ('Infusion date' for the last on-demand therapy form) Min ('Infusion date' for the first on-demand therapy form) + 1 day.
iii) Perioperative=Total dosage of perioperative/(On-study treatment period for perioperative/7).
On-study treatment period for perioperative = Max ('Regimen treatment stop date' for the last prophylaxis/perioperative page where Treatment Regimen = Perioperative coverage) Min ('Regimen treatment start date' for the first.
prophylaxis/perioperative page where Treatment Regimen = Perioperative coverage) + 1 day.
[d] Total number of infusion = Total number of infusion for prophylaxis therapy + Total number of infusion for perioperative therapy + Total number of infusion for on-demand therapy.
- Total number of infusion for prophylaxis or perioperative therapy: Sum of 'Total number of infusion'.
- Total number of infusion for on-demand therapy: Total number of unique combinations of 'Infusion date' and 'infusion time'.
[e] Mean dose per infusion = Total dose/Total number of infusion.
Source: ADYNOVATE South Korea Post-Marketing Surveillance (261603) final study report, Table 22.

ADYNOVATE Treatment in Pediatric Patients

Pediatric Patients Aged <2 Years (n=2): Overall, 2 patients received prophylaxis treatment. No patients in this age group received on-demand treatment or perioperative treatment.

Pediatric Patients Aged ≥2 to <12 Years (n=52): Overall, 50 patients received prophylaxis treatment, 2 patients received on-demand treatment, and 2 patients received perioperative treatment.

Pediatric Patients Aged ≥12 to <18 years (n=40): Overall, 40 patients received prophylaxis treatment, no patients received on-demand treatment, and 1 patient received perioperative treatment.

Table 11: Adynovate treatment status in pediatric patients

Age Group Variable	Patients	Prophylaxis Regimen Patients	On-demand Regimen Patients	Perioperative Regimen Patients
Pediatric Patients Aged <2 Years	**(N=2)**	**(N=2)**	**(N=0)**	**(N=0)**
Total dose[a] (IU)				
n	2	2	0	0
Mean (SD)	22,311.00 (6,563.37)	22,311.00 (6,563.37)	–	–
Min	17,670.00	17,670.00	–	–
Median	22,311.00	22,311.00	–	–
Max	26,952.00	26,952.00	–	–
Dosage per week[b,c] (IU/kg/wk)				
n	2	2	0	0
Mean (SD)	72.59 (15.79)	72.59 (15.79)	–	–
Min	61.43	61.43	–	–
Median	72.59	72.59	–	–
Max	83.76	83.76	–	–
Total number of infusion[d] (infusions)				
n	2	2	0	0
Mean (SD)	60.00 (4.24)	60.00 (4.24)	–	–
Min	57.00	57.00	–	–
Median	60.00	60.00	–	–
Max	63.00	63.00	–	–
Total number of infusion[d] (infusions, category), n (%)				
<30	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
≥30 ~ <50	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
≥50 ~ <70	2 (100.00)	2 (100.00)	0 (0.00)	0 (0.00)
≥70	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Total	2	2	0	0

Age Group Variable	Patients	Prophylaxis Regimen Patients	On-demand Regimen Patients	Perioperative Regimen Patients
Mean dose per infusion[c] (IU/infusion)				
n	2	2	0	0
Mean (SD)	376.66 (136.02)	376.66 (136.02)	–	–
Min	280.48	280.48	–	–
Median	376.66	376.66	–	–
Max	472.84	472.84	–	–
Mean dose per infusion[c] (IU/infusion, category), n (%)				
<1,000	2 (100.00)	2 (100.00)	0 (0.00)	0 (0.00)
≥1,000 ~ <2,000	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
≥ 2,000	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Total	2	2	0	0
Pediatric Patients Aged ≥2 to <12 Years	**(N=52)**	**(N=50)**	**(N=2)**	**(N=2)**
Total dose[a] (IU)				
n	52	50	2	2
Mean (SD)	36,515.04 (21,504.75)	36,218.86 (21,715.84)	43,919.50 (19,074.21)	2,063.00 (680.24)
Min	514.00	514.00	30,432.00	1,582.00
Median	31,520.00	31,520.00	43,919.50	2,063.00
Max	89,814.00	89,814.00	57,407.00	2,544.00
Dosage per week[b, c] (IU/kg/wk)				
n	52	50	2	2
Mean (SD)	63.66 (31.41)	64.09 (31.89)	52.79 (15.51)	292.78 (80.93)
Min	9.21	9.21	41.82	235.55
Median	62.87	62.87	52.79	292.78
Max	198.73	198.73	63.76	350.00

Age Group Variable	Patients	Prophylaxis Regimen Patients	On-demand Regimen Patients	Perioperative Regimen Patients
Total number of infusion[d] (infusions)				
n	52	50	2	2
Mean (SD)	43.94 (18.14)	43.68 (18.41)	50.50 (9.19)	3.00 (1.41)
Min	1.00	1.00	44.00	2.00
Median	48.00	48.00	50.50	3.00
Max	87.00	87.00	57.00	4.00
Total number of infusion[d] (infusions, category), n (%)				
<30	10 (19.23)	10 (20.00)	0 (0.00)	2 (100.00)
≥30 ~ <50	19 (36.54)	18 (36.00)	1 (50.00)	0 (0.00)
≥50 ~ <70	20 (38.46)	19 (38.00)	1 (50.00)	0 (0.00)
≥70	3 (5.77)	3 (6.00)	0 (0.00)	0 (0.00)
Total	52	50	2	2
Mean dose per infusion[c] (IU/infusion)				
n	52	50	2	2
Mean (SD)	843.14 (432.38)	840.09 (433.90)	919.30 (545.04)	713.50 (109.60)
Min	250.00	250.00	533.89	636.00
Median	748.00	748.00	919.30	713.50
Max	2,079.00	2,079.00	1,304.70	791.00
Mean dose per infusion[c] (IU/infusion, category), n (%)				
<1,000	37 (71.15)	36 (72.00)	1 (50.00)	2 (100.00)
≥1,000 ~ <2,000	13 (25.00)	12 (24.00)	1 (50.00)	0 (0.00)
≥2,000	2 (3.85)	2 (4.00)	0 (0.00)	0 (0.00)
Total	52	50	2	2

Age Group Variable	Patients	Prophylaxis Regimen Patients	On-demand Regimen Patients	Perioperative Regimen Patients
Pediatric Patients Aged ≥12 to <18 Years	**(N=40)**	**(N=40)**	**(N=0)**	**(N=1)**
Total dose[a] (IU)				
N	40	40	0	1
Mean (SD)	75,576.55 (33,672.94)	75,576.55 (33,672.94)	–	27,209.00 (-)
Min	2,332.00	2,332.00	–	27,209.00
Median	76,262.00	76,262.00	–	27,209.00
Max	153,648.00	153,648.00	–	27,209.00
Dosage per week[b, c] (IU/kg/wk)				
N	37	37	0	1
missing	3	3	–	–
Mean (SD)	58.65 (30.78)	58.65 (30.78)	–	404.56 (-)
Min	3.30	3.30	–	404.56
Median	58.82	58.82	–	404.56
Max	211.68	211.68	–	404.56
Total number of infusion[d] (infusions)				
N	40	40	0	1
Mean (SD)	44.45 (16.47)	44.45 (16.47)	–	26.00 (-)
Min	1.00	1.00	–	26.00
Median	48.00	48.00	–	26.00
Max	73.00	73.00	–	26.00
Total number of infusion[d] (infusions, category), n (%)				
<30	7 (17.50)	7 (17.50)	0 (0.00)	1 (100.00)
≥30 ~ <50	17 (42.50)	17 (42.50)	0 (0.00)	0 (0.00)
≥50 ~ <70	15 (37.50)	15 (37.50)	0 (0.00)	0 (0.00)
≥70	1 (2.50)	1 (2.50)	0 (0.00)	0 (0.00)
Total	40	40	0	1
Mean dose per infusion[e] (IU/infusion)				
N	40	40	0	1
Mean (SD)	1,739.76 (516.55)	1,739.76 (516.55)	–	1,046.50 (-)
Min	803.67	803.67	–	1,046.50
Median	1,635.33	1,635.33	–	1,046.50
Max	3,201.00	3,201.00	–	1,046.50
Mean dose per infusion[e] (IU/infusion, category), n (%)				
<1,000	1 (2.50)	1 (2.50)	0 (0.00)	0 (0.00)
≥1,000 ~ <2,000	27 (67.50)	27 (67.50)	0 (0.00)	1 (100.00)
≥2,000	12 (30.00)	12 (30.00)	0 (0.00)	0 (0.00)
Total	40	40	0	1

max=maximum; min=minimum; N=number of patients; n=number of patients per criterion; SD=standard deviation; wk=week.
Denominator of percentage is the number of 'Total'.

[a] Total dose = Total dose of prophylaxis therapy + Total dose of perioperative therapy + Total dose of on-demand therapy
- Total dose of prophylaxis or perioperative therapy: Sum of total dose (Total dose='Total number of infusion' * 'Total dose per infusion ([IU])
- Total dose of on-demand therapy: Sum of on-demand therapy for on-demand patient and on-demand therapy for prophylaxis patient
On-demand therapy for on-demand patient=Sum of 'Total dose per infusion (IU)' for all entries on the On Demand Therapy page for this patient.
On-demand therapy for prophylaxis patient=Sum of 'Total dose (IU)' from Administration for bleeding during Prophylaxis.

[b] Dosage per week: Total dosage/(On-study treatment period/7)

i) Total dosage = Total dosage of prophylaxis therapy + Total dosage of perioperative therapy + Total dosage of on-demand therapy
- Total dosage of prophylaxis or perioperative therapy: Sum of total dosage (Total dosage='Total number of infusion' + 'Dosage per infusion [IU/kg]')
- Total dosage of on-demand therapy: Total dosage of the On-Demand therapy + Total dosage of Administration for bleeding during Prophylaxis

Total dosage of the On-Demand Therapy = Sum of 'Dosage per infusion (IU/kg)', Total dosage of Administration for bleeding during Prophylaxis = Sum of Total dosage/Body weight at baseline.

ii) On-study treatment period = Max ('Regimen treatment stop date' for the last prophylaxis/perioperative form, 'Infusion Date' for the last on-demand therapy form) Min ('Regimen treatment start date' for the first prophylaxis/perioperative form, 'Infusion Date' for the first on-demand therapy form) + 1.

c Dosage per week by treatment regimen

i) Prophylaxis=Total dosage of prophylaxis/(On-study treatment period for prophylaxis/7)

On-study treatment period for prophylaxis= Max ('Regimen treatment stop date' for the last prophylaxis/perioperative page where Treatment Regimen = Prophylaxis) - Min ('Regimen treatment start date' for the first prophylaxis/perioperative page where Treatment Regimen = Prophylaxis) + 1 day

ii) On-demand=Total dosage of on-demand/(On-study treatment period for on-demand/7)

On-study treatment period for on-demand= Max ('Infusion date' for the last on-demand therapy form) - Min ('Infusion date' for the first on-demand therapy form) + 1 day

iii) Perioperative=Total dosage of perioperative/(On-study treatment period for perioperative/7)

On-study treatment period for perioperative = Max ('Regimen treatment stop date' for the last prophylaxis/perioperative page where Treatment Regimen = Perioperative coverage) - Min ('Regimen treatment start date' for the first prophylaxis/perioperative page where Treatment Regimen = Perioperative coverage) + 1 day

d Total number of infusion = Total number of infusion for prophylaxis therapy + Total number of infusion for perioperative therapy + Total number of infusion for on-demand therapy

- Total number of infusion for prophylaxis or perioperative therapy: Sum of 'Total number of infusion'.
- Total number of infusion for on-demand therapy: Total number of unique combinations of 'Infusion date' and 'infusion time'.

e Mean dose per infusion = Total dose/Total number of infusion.

Source: Table 2.15.1, Table 2.15.2, and Table 2.15.3.

Effectiveness Assessment for Prophylaxis

The effectiveness evaluation in patients who received ADYNOVATE for prophylaxis was based on the annualized bleeding rate (ABR) while on prophylaxis and the effectiveness of ADYNOVATE on-demand use to control breakthrough bleeds.

A total of 314 patients were treated with ADYNOVATE for prophylaxis. Of these, 239 (76.11%) patients did not bleed during both prophylaxis-only exposure period and the prophylaxis and bleed-control exposure period.

The total number of bleeds among patients with at least 1 bleed (75 patients) was 163. Of these, 60.74% (99/163 bleeds) required 1 ADYNOVATE infusion, 26.99% (44/163 bleeds) required 2 infusions, and 12.27% (20/163 bleeds) required 3 or more infusions. The physician assessment of effectiveness was available for 151 of the 163 bleeds. The assessment was "Excellent" for 70.86% (107/151 bleeds) and "Good" for 29.14% (44/151 bleeds).

The ABR was calculated to provide a standardized measure of effectiveness. During the prophylaxis-only exposure period, the mean (SD) ABR was 1.70 (5.05) bleeds/year and during the prophylaxis and bleed-control exposure period, the mean (SD) ABR was 1.38 (3.49) bleeds/year.

Effectiveness Assessment for Prophylaxis in Pediatric Patients

Pediatric Patients Aged <2 Years: Two patients aged <2 years were treated with ADYNOVATE for prophylaxis. Each patient had 1 bleed during the prophylaxis-only exposure period and the prophylaxis and bleed-control exposure period (ie, the total number of bleeds over the 2 periods was 2). These 2 breakthrough bleeds required 1 ADYNOVATE infusion. The physician's assessment of effectiveness of on-demand treatment was "Good" for these 2 bleeds.

The mean (SD) of ABR was 2.01 (0.03) bleeds/year during both the prophylaxis-only exposure period and the prophylaxis and bleed-control exposure period.

Pediatric Patients Aged ≥2 to <12 Years: A total of 50 patients were treated with ADYNOVATE for prophylaxis. Of these, 37 (74.00%) patients did not bleed during both the prophylaxis-only exposure period and the prophylaxis and bleed-control exposure period. The total number of bleeds among

patients with at least 1 bleed (13 patients) was 23. Of these bleeds, 52.17% (12/23 bleeds) required 1 ADYNOVATE infusion, 26.09% (6/23 bleeds) required 2 infusions, and 21.74% (5/23 bleeds) required 3 or more infusions. The physician's assessment of effectiveness of on-demand treatment was available for 13 bleeds; the assessment was "Excellent" in 53.85% (7/13 bleeds) and "Good" in 46.15% (6/13 bleeds). The mean (SD) of ABR was 1.14 (2.60) bleeds/year during prophylaxis-only exposure period and 1.07 (2.49) bleeds/year during prophylaxis and bleed-control exposure period.

Pediatric Patients Aged ≥12 to <18 Years: A total of 40 patients were treated with ADYNOVATE for prophylaxis. Of these, 31 (77.50%) patients did not bleed during both the prophylaxis-only exposure period and the prophylaxis and bleed-control exposure period. The total number of bleeds among patients with at least 1 bleed (9 patients) was 26. Of these bleeds, 57.69% (15/26 bleeds) required 1 ADYNOVATE infusion, 26.92% (7/26 bleeds) required 2 infusions, and 15.38% (4/26 bleeds) required 3 or more infusions. The physician's assessment of effectiveness of on-demand treatment was available for all 26 bleeds; the assessment was "Excellent" in 42.31% (11/26 bleeds) and "Good" in 57.69% (15/26 bleeds).

The mean (SD) of ABR was 1.62 (3.62) bleeds/year during the prophylaxis-only exposure period and 1.49 (3.26) bleeds/year during prophylaxis and bleed-control exposure period.

Effectiveness Assessment for On-demand Treatment

The effectiveness evaluation for patients who received ADYNOVATE as on-demand treatment was based on the ability of ADYNOVATE to control bleeds.

Overall, 23 patients were treated with ADYNOVATE as on-demand treatment; the total number of bleeds in these patients was 322. Of these bleeds, 70.81% (228/322 bleeds) were controlled with 1 ADYNOVATE infusion, 18.32% (59/322 bleeds) with 2 infusions, and 10.87% (35/322 bleeds) with 3 or more infusions. The physician assessment of effectiveness was available for 289 of the 22 bleeds; the assessment was "Excellent" in 36.33% (105/289 bleeds), "Good" in 60.55% (175/289 bleeds), "Fair" in 2.77% (8/289 bleeds), and "None" in 0.35% (1/289 bleed).

Effectiveness Assessment for On-demand Regimen in Pediatric Patients

Two patients were treated with ADYNOVATE as on-demand treatment. These subjects were aged ≥2 to <12 years. The total number of bleeds experienced by both patients was 31. Of these bleeds, 87.10% (27/31 bleeds) required 1 ADYNOVATE infusion and 12.90% (4/31 bleeds) required 3 or more infusions. The physician's assessment of effectiveness of on-demand treatment was available for 4 of these 31 bleeds; the assessment was "Good" for all (100.00%).

Effectiveness Assessment for Perioperative Use

The effectiveness evaluation for patients who received ADYNOVATE for perioperative use was based on the physician assessment of the effectiveness of ADYNOVATE infusions in controlling bleeding. A total of 9 patients received ADYNOVATE as perioperative treatment. Five (55.56%) patients were treated with ADYNOVATE before surgery, 1 (11.11%) patient was treated with ADYNOVATE during surgery, and 8 (88.89%) patients were treated with ADYNOVATE after surgery. Of note, a patient could have had more than 2 perioperative treatment phases (before surgery, during surgery, and after surgery).

The effectiveness assessment for perioperative treatment was available for 5 patients. The assessment was "Excellent" in 1 of 5) (20%) patients, "Good" in 3 of 5 (60%) patients, and "Fair" in 1 of 5 (20%) patients.

Effectiveness Assessment for Perioperative Use in Pediatric Patients

Pediatric Patients Aged <2 Years: There were no patients in this age group who received ADYNOVATE as perioperative treatment.

Pediatric Patients Aged ≥2 to <12 Years: Two patients years were treated with ADYNOVATE as perioperative treatment. One patient was treated with ADYNOVATE before and after surgery and the other patient was treated with ADYNOVATE during and after surgery. The effectiveness assessment was available only for 1 patient. The effectiveness assessment for this patient was "Good".

Pediatric Patients Aged ≥12 to <18 Years: One patient aged was treated with ADYNOVATE as perioperative treatment, before and after the surgery. The effectiveness assessment for this patient was "Fair."

Assessor's comment

Most patients (239/314 patients, 76.11%) receiving ADYNOVATE as prophylaxis did not bleed during both the prophylaxis-only exposure period and the prophylaxis and bleed-control exposure period. The ABR was below 2 bleeds/year in patients who received ADYNOVATE as prophylaxis. Most of the breakthrough bleeds that occurred during the prophylaxis period (143/163 bleeds) were controlled with 1 ADYNOVATE infusion (99/163 bleeds, 60.74%) or with 2 ADYNOVATE infusions (44/163 bleeds, 26.99%). The physician's effectiveness assessment, which was available for 151 of the 163 bleeds; was "Excellent" for 70.86% (107/151 bleeds) and Good" for 29.14% (44/151 bleeds).

Patients receiving on-demand treatment (23 patients) most bleeds (228/322 bleeds, 70.81%) were effectively treated with only 1 ADYNOVATE infusion.

For patients in the perioperative treatment group 5 of 9 patients (55.56%) were treated with ADYNOVATE before surgery, 4 patients (80.00%) received a single treatment, 1 patient (20%) needed 2 infusions.

Regarding **children**, a total of 50 patients aged between 2 years and 12 years were treated with ADYNOVATE for prophylaxis. Most patients (74.00%, 37/50 patients) did not bleed. 13 patients (26.00%) had one or more bleeds (total number of bleeds among all patients was 23). During prophylaxis-only exposure period, the mean (± SD) of annualized bleed rate was 1.14 ± 2.60 bleeds/year. During prophylaxis and bleed-control exposure period, the mean (± SD) of annualized bleed rate was 1.07 ± 2.49 bleeds/year. Of 23 bleeds experienced by the 13 patients, 52.17% (12/23 bleeds) required one ADYNOVATE infusion, 26.09% (6/23 bleeds) required two infusions, and 21.74% (5/23 bleeds) required 3 or more infusions. For 13 bleeds of these 23 bleeds, a physician assessment of effectiveness of on-demand treatment (prophylaxis and on-demand treatment group) was available, and the assessment was 'Excellent' in 53.85% (7/13 bleeds) and 'Good' in 46.15% (6/13 bleeds).

A total of 40 patients aged between 12 years and 18 years were treated with ADYNOVATE for prophylaxis. Of these patients, 77.50% (31/40 patients) had zero bleeds and 22.50% (9/40 patients) had one or more bleeds. Of the 9 patients who had at least one bleed, the total number of bleeds among all patients was 26. These results are same during both prophylaxis-only exposure period and bleed-control exposure period.

Of the 2 children aged ≥2- <12 years in the on-demand treatment group, 87,1 % (27/31 bleeds) required 1 infusion, 12.90% (4/31 bleeds) required three infusions.

A total of 2 patients (≥2 -<12 years) treated with ADYNOVATE received perioperative treatment. Among the 2 patients, 1 patient was treated with ADYNOVATE before and after surgery and 1 patient was treated with ADYNOVATE during and after surgery. Each 1 patient treated with ADYNOVATE before surgery and during surgery received a single infusion. Among the 2 patients treated with ADYNOVATE after surgery, 1 patient received a single infusion, and 1 patient received a single treatment up of 3 or more infusions. During prophylaxis and bleed-control exposure period, the mean (± SD) of annualized bleed rates was 1.49 ± 3.26 bleeds/year. Only 1 patient aged between 12 years and 18 years treated with ADYNOVATE received perioperative treatment before and after surgery. Before surgery, this patient received a single infusion before surgery. After surgery, this patient received 2 treatments, consisting of a single infusion, a single treatment, consisting of two infusions, and 3 treatments, consisting of 3 or more infusions after surgery. For this patient, effectiveness assessment for perioperative treatment was 'Fair'

To sum up, the number of paediatric patients included is considerable and allows an individual assessment of efficacy and safety in this subgroup on a descriptive basis. The results of the effectiveness evaluation of ADYNOVATE in patients aged <2 years to 18 years were consistent with those obtained in the overall population. In general, the effectiveness results of this study complement the findings from previous clinical trials. Nevertheless, results need to be interpreted cautiously due to the shortcomings in relation to definition of bleeding events.

Safety results

Overall, 20 (5.92%) patients had 23 AEs; the majority (21 AEs) were unexpected. Four (1.18%) patients had 4 adverse drug reactions (ADRs); of these, 2 ADRs in 2 (0.59%) patients were unexpected (rhinitis allergic and pyrexia, Table 4). Four (1.18%) patients had 4 serious adverse events (SAEs), all unexpected SAEs but none was an ADR.

Table 12: Summary of adverse events

	Safety Follow-up Analysis Set (N=338)		
	Number (and Percent) of Patients with Events, n (%)[a]	95% CI[b] for Expected Percent of Patients with an Event	Number of Events (%)[c]
Adverse events (AEs)	20 (5.92)	(3.65, 8.99)	23 (100.00)
Adverse drug reaction (ADRs)[d]	4 (1.18)	(0.32, 3.00)	4 (17.39)
Serious adverse event (SAEs)	4 (1.18)	(0.32, 3.00)	4 (17.39)
Serious adverse drug reaction (SADRs)	0 (0.00)	-	0 (0.00)
Unexpected adverse event (Unexpected AEs)[e]	18 (5.33)	(3.19, 8.29)	21 (91.30)
Unexpected adverse drug reaction (Unexpected ADRs)	2 (0.59)	(0.07, 2.12)	2 (8.70)
Unexpected serious adverse events (Unexpected SAEs)	4 (1.18)	(0.32, 3.00)	4 (17.39)
Unexpected serious adverse drug reactions (Unexpected SADRs)	0 (0.00)	-	0 (0.00)

ADRs=adverse drug reactions; AEs=adverse events; CI=confidence interval; n=number of patients; SADRs=serious adverse drug reactions; SAEs=serious adverse events.

[a] Denominator of percentage is the number of patients in the safety follow-up analysis set.

[b] 95% CI is calculated using Clopper Pearson exact method.

cDenominator of percentage is the total number of events in the safety follow-up analysis set.

[d] Adverse drug reaction=Adverse events whose relationship to ADYNOVATE is 'Certain', 'Probable/Likely', 'Possible', 'Conditional/Unclassified', 'Unassessible/Unclassifiable'.

[e] Unexpected adverse event=An AE that is not listed in the package insert.

Source: ADYNOVATE South Korea Post-Marketing Surveillance (261603) final study report, Table 24.

The most frequently reported AEs were haemarthrosis and pyrexia, which were reported in 2 (0.59%) patients each. Other preferred terms (PTs) were reported by 1 (0.3%) patient each. Most of the AEs were of mild severity (18 AEs), 4 AEs were moderate, and 1 AE (appendicitis) was severe. The AE relationship to ADYNOVATE treatment was assessed as "Unlikely" for most AEs (19 AEs), "Unassessible/Unclassifiable" for 2 AEs (rhinitis allergic and diarrhoea), and "Certain" and Conditional/Unclassified" for 1 AE each (pyrexia and headache, respectively). For most AEs, the action taken with ADYNOVATE was "Dose not changed" (18 AEs), dose was increased for 3 AEs, interrupted for 1 AE, and 1 AE caused drug withdrawal. All AEs recovered/resolved, except 1 AE that recovered/resolved with sequelae (rhinitis allergic), and 1 AE that did not recover/resolve (dizziness).

There were no AEs with a fatal outcome.

Summary of Adverse Events in Pediatric Patients

Pediatric Patients Aged <2 Years (n=2): One (50.00%) patient had an AE of nasopharyngitis. Pediatric Patients Aged ≥2 to <12 Years (n=52): Six (11.54%) patients had 9 AEs. Preferred terms (arthralgia, haemarthrosis, joint swelling, balanoposthitis, testicular retraction, anaemia, pyrexia, rhinitis allergic, and nail dystrophy) were reported by 1 (1.92%) patient each. The event of rhinitis allergic was reported as an ADR (1.92% of patients in this age classification).

Pediatric Patients Aged ≥12 to <18 years (n=40): A total of 4 (10.00%) patients had 4 AEs. Preferred terms (COVID-19, haemarthrosis, headache, and haematoma) were reported by 1 (2.50%) patient each. The event of headache was reported as an ADR (2.50% of patients in this age classification).

Adverse Drug Reactions

Overall, 4 (1.18%) patients had 4 ADRs. None of these ADRs was serious and 2 occurred in pediatric patients (rhinitis allergic and headache).

Two of the 4 ADRs were unexpected (rhinitis allergic and pyrexia). These 2 unexpected ADRs were of mild severity and one (pyrexia) was assessed as having a "Certain" relationship with ADYNOVATE treatment.

Table 13: Listing of adverse drug reactions

Age Group	Sex	System Organ Class (SOC)	Preferred Term (PT)	Serious	Severity	Relationship by the Investigator	Causal Relationship with Others	Action Taken	Outcome	Expectedness
≥12 to <18 years		Nervous system disorders	Headache	No	Mild	Conditional/ Unclassified	Concomitant medication	Dose not changed	Recovered/ resolved	Expected AE
≥2 to <12 years		Respiratory, thoracic and mediastinal disorders	Rhinitis allergic	No	Mild	Unassessible/ Unclassifiable	Concomitant medication	Dose not changed	Recovered/ resolved with sequelae	Unexpected AE
≥18 to <65 years		Gastrointestinal disorders	Diarrhoea	No	Mild	Unassessible/ Unclassifiable	N/A	Dose not changed	Recovered/ resolved	Expected AE
≥18 to <65 years		General disorders and administration site conditions	Pyrexia	No	Mild	Certain	N/A	Drug withdrawn	Recovered/ resolved	Unexpected AE

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; N/A=not applicable; PT=preferred term; SOC=system organ class.
Adverse drug reactions: All AEs whose relationship to ADYNOVATE was 'Certain', 'Probable/Likely', 'Possible', 'Conditional/Unclassified', 'Unassessible/Unclassifiable'.
System organ classes and PTs were coded using MedDRA version 26.1.
Source: ADYNOVATE South Korea Post-Marketing Surveillance (261603) final study report, Table 36.

Serious Adverse Events

Overall, 4 (1.18%) patients had 4 SAEs. Two of these SAEs occurred in pediatric patients (haemarthrosis and haematoma).

Table 14: Listing of serious adverse events

Age Group	Sex	System Organ Class (SOC)	Preferred Term (PT)	SAE Detail	Severity	Relationship by the Investigator	Causal Relationship with Others	Action Taken	Expectedness
≥18 to <65 years		Gastrointestinal disorders	Haematochezia	Requiring hospitalization or existing hospitalization prolonged	Moderate	Unlikely	Other - unknown	Dose increased	Unexpected AE
≥18 to <65 years		Infections and infestations	Appendicitis	Requiring hospitalization or existing hospitalization prolonged	Severe	Unlikely	Other – unknown (unexpected symptom)	Drug interrupted	Unexpected AE
≥12 to <18 years		Musculoskeletal and connective tissue disorders	Haemarthrosis	Requiring hospitalization or existing hospitalization prolonged	Moderate	Unlikely	Concurrent Disease	Dose increased	Unexpected AE
≥12 to <18 years		Vascular disorders	Haematoma	Requiring hospitalization or existing hospitalization prolonged	Moderate	Unlikely	Concurrent Disease	Dose increased	Unexpected AE

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SAE=serious adverse event; SOC=system organ class.
System organ classes and PTs were coded using MedDRA version 26.1.
Source: ADYNOVATE South Korea Post-Marketing Surveillance (261603) final study report, Table 38.

Factor VIII Antibodies

During this study, no patient reported developing FVIII antibodies after baseline.

Logistic regression response and predictor variables

The result of a multivariate logistic regression model showed that there was no significant association between the probability of RHN AEs and on several factors

Table 15: Logic regression of occurrence of AEs in renal, hepatic, nervous system on age group, cumulative dosage, and baseline renal, hepatic and nervous system conditions

Risk factor	Categories	Number of patients in this category	Number (%) of patients with an RHNAE
Exploratory analysis for categorical variables			
SFAS patients with no missing values of input variables	N/A	316	1 (0.32)
Baseline Renal, Hepatic, or Neurological Disorder	No	303	1 (0.33)
	Yes	13	0 (0.00)
Age Group	Infants & toddlers(<2 years), or Children (≥2 ~ <12 years)	54	0 (0.00)
	Adolescents (≥12 ~ <18 years)	37	0 (0.00)
	Adults (≥18 ~ <65 years)	225	1 (0.44)

Logistic regression (generalized additive model) results

Type III tests of fixed effects

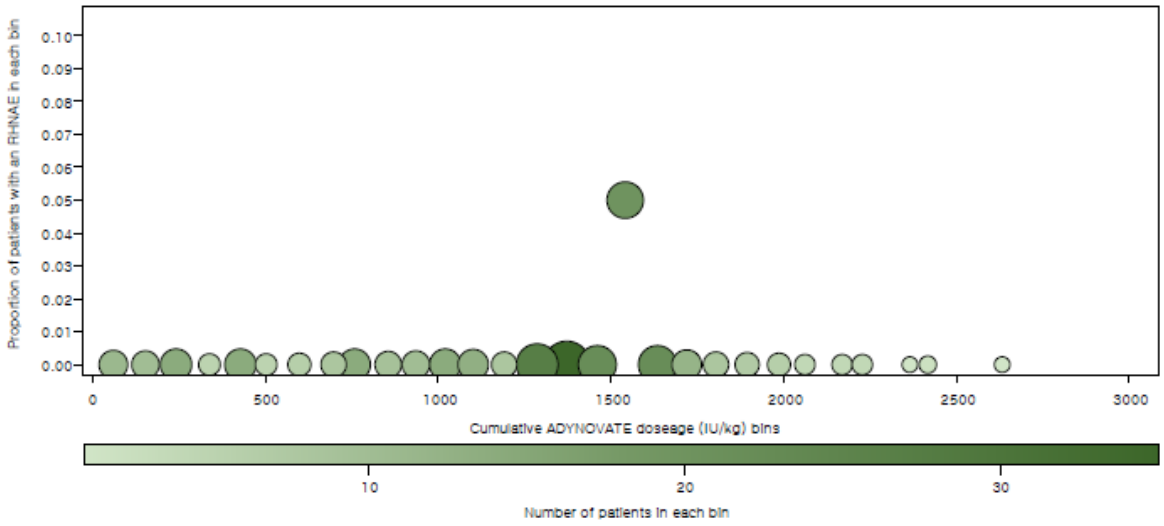
Variable	Numerator degrees of freedom	Denominator degrees of freedom	F-statistic	Pr>F
Cumulative dosage (IU/kg)	3	309	0.00	1.0000

Risk factor	Categories	Number of patients in this category	Number (%) of patients with an RHNAE	
Age Group	2	309	0.00	0.9998
Baseline Renal, Hepatic, or Neurological Disorder	1	309	0.00	0.9939

Dependent variable(RHNAE): the occurrence of an AE in the renal, hepatic, or neurological system organ classes (SOCs) (Probability modeled is 'Yes').
Multiple logistic regression generalized additive model: RHNAE = BLRHND + age group + spline(Cumulative exposure to ADYNOVATE (IU/kg)),
- BLRHND: Baseline renal, hepatic, or neurological disorder status
- spline(Cumulative exposure to ADYNOVATE (IU/kg)) is a piecewise linear spline with knots at the first quartile, median, and third quartile to allow for potential nonlinear relationship.
Pr>F is the p-value for testing the null hypothesis that there is no effect of the covariate on the probability of a patient having a Renal, Hepatic, or Neurological AE.

In addition, exploratory analysis of the relationship between the probability of an AE and cumulative dosage was performed. There was no trend of the probability of an AE between RHN AEs and cumulative dosage of ADYNOVATE.

Figure 1: relationship between the probability of an AE and cumulative dosage of Adynovate



The values of Cumulative ADYNOVATE dosage (IU/kg) were divided into 30 evenly-spaced bins.
The number of patients in each bin is represented by the size and color of the plot symbol: darker colors and larger dots represent a larger sample size in the dosage bin.
The proportion of patients in each bin with a Renal, Hepatic, or Neurological AE (RHNAE) was calculated as an estimate of the probability of a patient having a RHNAE.

Assessor's comment

338 patients were included in the safety assessment. The majority of patients were male (99.41%). The mean (± SD) of FVIII levels at baseline was 7.33 (± 13.18). Most bleeding episodes per patient within the last 12 months by severity was 'Mild' (3.84 ± 8.01). There was no patient who had a history of thromboembolism. 28 patients (8.59%) had family history of inhibitors. Among 338 patients, 13 patients (3.85%) had history of inhibitor development, a history of inhibitor titer level, respectively, and all patients had FVIII treatment history. No patient reported ADYNOVATE as the FVIII product used at the time of inhibitor detection. During the observation period, a total of 23 AEs were reported from 20 patients (5.92%).

Among 23 AEs, 2 AEs were reported from patients who were newly prescribed with ADYNOVATE, and 21 AEs were reported from patients who were previously treated with ADYNOVATE before enrolled in this PMS study. The most frequently reported AEs classified into PT were 'Haemarthrosis', 'Pyrexia' (2 events, 0.59%, respectively), and other PTs were reported in 1 event, respectively. Among the reported 23 AEs, a total of 4 ADRs were reported from 4 patients (1.18%). The 4 ADRs were classified into PT as 'Pyrexia', 'Diarrhoea', 'Headache', and 'Rhinitis allergic' (1 event, 0.30%, respectively). Among the reported 23 AEs, 21 AEs except for 1 event (0.30%) of 'Diarrhoea' and 'Headache', respectively, are classified as unexpected AEs, but only 2 AEs ('Pyrexia' and 'Rhinitis allergic') were reported as unexpected ADRs.

A total of 4 SAEs were reported from 4 patients (1.18%), and reported SAEs were classified into PT as 'Haematochezia', 'Appendicitis', 'Haemarthrosis', and 'Haematoma'. All 4 SAEs were unexpected SAEs but not unexpected SADRs.

The severity of the reported 23 AEs was most (18 AEs) 'Mild'. The AE's relationship to ADYNOVATE was 19 events of 'Unlikely', 2 events of 'Unassessible/ Unclassifiable', 1 event of 'Certain', 'Conditional/Unclassified', respectively. Physician evaluated AE's causal relationship other than ADYNOVATE as 10 events of 'Other', 7 events of 'Not applicable', and 3 events of 'Concomitant medication' and 'Concurrent disease', respectively. After AE occurred, action taken on ADYNOVATE was 18 events of 'Dose not changed', 3 events of 'Dose increased', and 1 event of 'Drug interrupted', 'Drug withdrawn'. Among the reported 23 AEs, only 1 AE was not recovered or resolved, and others were recovered.

Only 2 ADR occurred in pediatric patients (rhinitis allergic and headache). These were resolved by end of study. Two of 4 SAEs occurred in pediatric patients (haemarthrosis and haematoma). Action taken was a drug increase.

To estimate the occurrence of an AE in the renal, hepatic, or neurological system organ classes (RHNAE) the Applicant used a multivariate logistic regression model which is no further described. According to the Applicant this model showed that there was no significant association between the probability of RHN AEs and cumulative Adynovate dosage. Regarding Figure 30 one bin (1600 IU/kg) seems to have a higher proportion of RHNAR. The meaning for pediatric patients is not fully clear but does not seem reason for concern at this stage.

Overall ADYNOVATE was well tolerated and no new safety concerns were identified during this PMS in patients with hemophilia A in South Korea. So far, no new safety findings emerge for the pediatric population and no concerns arise from the data presented.

2.3.3. Discussion on clinical aspects

As part of this Article 46 procedure, the MAH submitted the final report of study 261603 together with a Clinical Overview Addendum. Study 261603 was a 6-year, multicenter, prospective, non-interventional post marketing surveillance study conducted in South Korea with the goal to investigate the safety and hemostatic effectiveness of ADYNOVATE in routine clinical practice. Patients aged <18 years were also included.

This study was required by Korea's Ministry of Food and Drug Safety (MFDS) according to 'Standards for Re-examination of New Drugs' to assess the safety and describe hemostatic effectiveness for the approved local label of ADYNOVATE in a real-world setting in South Korea.

Data was collected between 31 January 2018 and 30 January 2024, with ADYNOVATE treated patients under standard clinical care in South Korea. In this study, physicians collected the data of safety and effectiveness at 0 month (baseline), 1 month and 6 months.

The primary objective was to characterize the safety of ADYNOVATE when used in standard clinical practice of hemophilia A patients in South Korea. The secondary objectives were to monitor long term safety of ADYNOVATE in pediatric and adult patients with hemophilia A and to evaluate hemostatic effectiveness in patients with hemophilia A receiving ADYNOVATE under standard clinical care in South Korea. In how far the 6 months duration is sufficient to capture long-term safety is not further commented on, but it seems rather short compared to regulatory standard in the EU.

Inclusion criteria of the study were patients with a diagnosis of hemophilia A who were newly prescribed with ADYNOVATE or who already have been prescribed ADYNOVATE according to the physician's judgment, if 1. The patient or legally authorized representative has given written informed consent to participate in the study and 2. The patient is indicated for treatment according to the ADYNOVATE South Korea prescribing information (PI). A comparison between the ADYNOVATE

prescribing information (PI) in South Korea and the European Union was lacking. This raised questions about whether the indications for use, target population, dosage, and method of administration are the same between the two regions. Upon request potential discrepancies in these areas were discussed to ensure the study's findings are applicable across different regions. As the South Korean treatment recommendations are basically similar to the EU recommendations, this issue is resolved.

The study did not include hypothesis testing and no formal sample size calculation was provided. According to the protocol, the target sample size was 330 patients.

A total of eCRFs of 339 patients were collected and 338 patients with hemophilia A were included in safety assessment and effective assessment. Of 338 patients, 336 (99.41%) were male and 2 (0.59%) were female. Included was also a subset of paediatric subjects (n=2 infants <2years, n=52 children aged 2 to <12 years, n=40 adolescents >12 years) for on demand, perioperative or prophylactic treatment according to daily clinical practice and patient needs. The number of paediatric patients included is considerable and allows an individual assessment of efficacy and safety in this subgroup on a descriptive basis.

Eleven pediatric patients were newly prescribed with ADYNOVATE; 5 patients were aged ≥2 to <12 years and 6 patients were aged ≥12 to <18 years. Eighty-three pediatric patients were previously treated with ADYNOVATE; 2 patients were aged <2 years, 47 patients were aged ≥2 to <12 years, and 34 patients were aged ≥12 to <18 years.

Baseline conditions (hemophilia A diagnosis, bleeding episodes, history of inhibitor development, history of inhibitor titer level, FVIII levels, FVIII treatment history, ..) were evaluated in the overall population as well as for pediatric patients separately.

Withdrawal rates were higher among newly prescribed patients (6/29, 20%) compared to those who had been previously treated with ADYNOVATE (24/310, 7%). This difference is expected, as patients who cannot tolerate the drug are more likely to discontinue it early, meaning they are no longer included in the previously treated group.

Assessment of effectiveness was done by a) Bleeding Assessment (each individual bleed, spontaneous or traumatic, will be recorded in patient’s diary, and/or recorded in study physician/nurse/clinic notes) b) the number of ADYNOVATE infusions needed for the treatment of bleeding episodes (determined by the patient, his/her caregiver, and/or clinician treating the patient, and is based upon the patient’s response to treatment, using the Efficacy Rating Scale for Treatment of Bleeding Episodes) c) the overall hemostatic effectiveness rating at resolution of bleed (for each bleeding episode: type of bleed, date and time of onset of bleed, of each infusion of ADYNOVATE required achieving adequate hemostasis, of resolution of bleeding episode and overall clinical efficacy rating).

The study report did not include a clear definition of "bleed/bleeding,". Lack of definition could have led to inconsistencies in reporting. A standard definition should have been established beforehand. This issue is noted, however as this study is regarded as supplementary information and has limited impact on the overall B/R balance of Adynovi no concerns are raised.

The evaluation of ADYNOVATE's effectiveness in treating hemophilia patients showed positive outcomes across different age groups and treatment scenarios. In the overall population, 76.11% of patients on ADYNOVATE prophylaxis did not experience any bleeding. The annualized bleeding rate (ABR) was below 2 bleeds per year. Most breakthrough bleeds were controlled with one or two ADYNOVATE infusions, with physicians rating the treatment as "Excellent" for 70.86% of bleeds.

In on-demand treatment, 70.81% of bleeds were effectively treated with a single infusion. In the perioperative treatment group, most patients required only one infusion before surgery.

Among children aged 2 to 12 years, 74% did not bleed while on prophylaxis, with a low ABR. Similarly, 77.5% of patients aged 12 to 18 years had no bleeds. For those who did bleed, most were managed with one or two infusions.

Overall, the effectiveness of ADYNOVATE in pediatric patients mirrored the positive results seen in the broader population, aligning with previous clinical trial findings. Nevertheless, efficacy results need to be interpreted cautiously due the shortcomings regarding lack of general definition of bleeding event.

The safety evaluation was conducted using safety data collected on the incidence of all types of AEs for the SFAS overall and by subgroup; the incidence and frequency of AEs, further classified by serious, severity, and reported causal relationship to ADYNOVATE; all AEs that occurred during or after first ADYNOVATE administration (categorization according to the MedDRA); inhibitor titers for FVIII antibodies by incidence and by high and lower titer categories; occurrence of AE by demographics and baseline characteristics and abnormal laboratory results.

In the safety assessment of ADYNOVATE involving 338 patients, the treatment was generally well tolerated. The mean baseline FVIII level was 7.33 IU/dL, and most recent bleeding episodes were mild. No patients had a history of thromboembolism, but 8.59% had a family history of inhibitors, and 3.85% had a personal history of inhibitor development. During the study, 23 adverse events (AEs) were reported in 20 patients (5.92%), with the most common being hemarthrosis and pyrexia. Only four adverse drug reactions (ADRs) were reported, including fever, diarrhea, headache, and allergic rhinitis.

Four serious adverse events (SAEs) were reported, none of which were considered related to ADYNOVATE. Most AEs were mild, and most patients did not require changes to their ADYNOVATE dosage.

In pediatric patients, two ADRs (allergic rhinitis and headache) and two SAEs (hemarthrosis and hematoma) occurred, all of which were resolved by the study's end. While headache is already included in section 4.8 of the SmPC, allergic rhinitis is not included yet. The MAH was asked to discuss a possible relationship with Adynovi and justify why inclusion of “allergic rhinitis” in section 4.8 of the SmPC is not necessary. According to the Applicant the reported case of allergic rhinitis was initially classified as "unassessible/unclassifiable". To comply with local regulations based on the World Health Organization’s causality assessment the case was recorded as "related" before the final determined causality assessment was completed. However, after further review determined that the allergic rhinitis was self-limited and not related to Adynovi, aligning with environmentally mediated allergies. A comprehensive search of Takeda's Global Safety Database from July 21, 2011, to August 30, 2024, identified four nonserious cases of rhinitis (two from South Korea, one from Brazil, and one from Germany). All events were consistent with upper respiratory infections or seasonal allergies, predominantly in children (3/4) and unlikely related to Adynovi, which is agreed.

To estimate the occurrence of an AE in the renal, hepatic, or neurological system organ classes (RHNAE) the Applicant used a multivariate logistic regression model which is no further described. According to the Applicant this model showed that there was no significant association between the probability of RHN AEs and cumulative Adynovate dosage. Regarding Figure 30, one bin (1600 IU/kg) seems to have a higher proportion of RHNAR, the meaning for pediatric patients is not fully clear but does not seem reason for concern at this stage.

In essence, results of study 261603 complement the findings from previous clinical trials.

3. Request for supplementary information

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

1. The applicant is asked to identify potential discrepancies (especially indication, target population, posology of administration) between the South Korean and EU product (information) and discuss them if necessary with regard to this study and applicability for the EU region.
2. The ADR allergic rhinitis is currently not included in the EU PI. The MAH should discuss a possible relationship with Adynovi and justify why inclusion of "allergic rhinitis" in section 4.8 of the SmPC is not necessary.

The timetable is a 30 day response timetable with clock stop

MAH responses to Request for supplementary information

Question 1

The applicant is asked to identify potential discrepancies (especially indication, target population, posology of administration) between the South Korean and EU product (information) and discuss them if necessary with regard to this study and applicability for the EU region.

Takeda Response 1

After reviewing both the European Union (EU) Summary of Product Characteristics (SmPC) and the South Korean package insert (PI), Takeda has concluded that while there are no major differences other than the indicated population, there are stylistic differences.

In the South Korean PI, ADYNOVATE is indicated in children, adolescents, and adults with hemophilia A, while the EU SmPC specifically indicates Adynovi treatment for patients 12 years and above with haemophilia A.

The language in the EU SmPC for prophylaxis states "twice weekly in 3-to-4-day intervals," while the South Korean PI states "2 times per week." This is one of multiple examples of stylistic differences. The meaning is the same, but there are slight differences in wording/approach. The minor differences in the South Korean PI are aligned more with the company position, while the language in the EU SmPC is aligned with the company position and the EU Core SmPC for Factor VIII products.

A summary of the differences between the EU SmPC and South Korean PI is shown in Table 2.a with key differences highlighted.

In South Korea, reimbursement criteria for medications significantly restrict actual medical practice, impacting the administration of ADYNOVATE for prophylaxis. The approved dose is 40-50 IU/kg body weight for individuals aged 12 years and above, and 55 IU/kg body weight for those under 12 years, to be administered twice per week. However, due to strict reimbursement limitations, the actual prophylaxis dose is capped at 20-30 IU/kg body weight regardless of age.

Table 16: Comparison of EU SmPC and South Korean PI

	EU SmPC			South Korean PI		
Indication	Treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia A (congenital factor VIII deficiency).			Antihemophilic Factor (Recombinant), PEGylated, is a human antihemophilic factor indicated in children, adolescents, and adults with hemophilia A (congenital factor VIII deficiency) for: • On-demand treatment and control of bleeding episodes • Perioperative management • Routine prophylaxis to reduce the frequency of bleeding episodes ADYNOVATE is not indicated for the treatment of von Willebrand disease.		
Prophylactic Treatment	Prophylaxis For long term prophylaxis, the recommended dose is 40 to 50 IU of ADYNOVI per kg bodyweight twice weekly in 3 to 4 day intervals. Adjustments of doses and administration intervals may be considered based on achieved FVIII levels and individual bleeding tendency.			Routine Prophylaxis Administer 40-50 IU per kg body weight 2 times per week in adolescents and adults (12 years and older). Administer 55 IU per kg body weight 2 times per week in children (< 12 years) with a maximum of 70 IU per kg. Adjust the dose based on the patient's clinical response.		
Haemorrhage/Bleeding Episode	**Degree of haemorrhage**	**FVIII level required (% or IU/dl)**	**Frequency of doses /duration of therapy**	**Type of Bleeding**	**Target FVIII level (IU/dL or % of normal)**	**Frequency of Doses/Duration of therapy**
	Early haemarthrosis, muscle bleeding or oral bleeding.	20–40	Repeat injections every 12 to 24 hours. At least 1 day, until the bleeding episode, as indicated by pain, is resolved or healing is achieved.	Minor Early hemarthrosis, mild muscle bleeding, or mild oral bleeding episode.	20–40	Frequency of dosing is 12-24 hours until the bleeding is resolved.
	EU SmPC			**South Korean PI**		
	More extensive haemarthrosis, muscle bleeding or haematoma.	30-60	Repeat injections every 12 to 24 hours for 3-4 days or more until pain and acute disability are resolved.	Moderate Muscle bleeding, moderate bleeding into the oral cavity, definite hemarthroses, and known trauma.	30-60	Frequency of dosing is 12-24 hours until the bleeding is resolved.
	Life threatening haemorrhages.	60-100	Repeat injections every 8 to 24 hours until threat is resolved.	Major Significant gastrointestinal bleeding, intracranial, intra-abdominal or intrathoracic bleeding, central nervous system bleeding, bleeding in the retropharyngeal or retroperitoneal spaces or iliopsoas sheath, fractures, head trauma.	60-100	Frequency of dosing is 8-24 hours until the bleeding is resolved.
	EU SmPC			**South Korean PI**		
Surgery	**Type of Surgical Procedure**	**FVIII Level Required (% or IU/dl)**	**Frequency of Doses/Duration of Therapy**	**Type of Surgery**	**Factor VIII Level Required (% of normal or IU/dL)**	**Frequency of Doses/Duration of Treatment**
	Minor Including tooth extraction.	30-60	Every 24 hours at least 1 day, until healing is achieved.	Minor Including tooth extraction.	30-60	Within one hour before surgery. Repeat after 24 hours if necessary (Repeat after 12~24 hours for patients <12 years of age). Single dose or repeat as needed until bleeding is resolved.
	Major	80-100 (pre - and postoperative)	Repeat injections every 8 to 24 hours until adequate wound healing, then continue therapy for at least another 7 days to maintain a factor VIII activity of 30% to 60% (IU/dl).	Major Intracranial, intra-abdominal, or intrathoracic surgery, joint replacement surgery.	80-100 (pre-and postoperative)	Within one hour before the operation to achieve 100% activity. Repeat every 8 to 24 hours (6 to 24 hours for patients <12 years of age) to maintain FVIII activity within the target range. Treat until adequate wound healing.

FVIII=factor VIII; PI=product information; SmPC=summary of product characteristics.

Assessment of Response

The Applicant`s review of the EU Summary of Product Characteristics (SmPC) and the South Korean package insert (PI) for ADYNOVATE reveals no major differences, aside from the indicated patient age groups. The South Korean PI includes children, adolescents, and adults with hemophilia A, whereas the EU SmPC specifies patients aged 12 years and above. Stylistic differences, such as the wording for dosing schedules are considered negligible. As the South Korean treatment recommendations are basically similar to the EU recommendations, the study 261603 results are applicable also to the EU population.

Conclusion:

Issue resolved.

Question 2

The ADR allergic rhinitis is currently not included in the EU PI. The applicant should submit a variation in order to update the PI or justify why this is not necessary.

Takeda Response 2

Takeda would like to clarify that the case of allergic rhinitis reported from South Korea was first determined to be “unassessible/unclassifiable”, but to be in compliance with the local regulations the reported finding was initially recorded as "Related" as per the World Health Organization causality assessment, even before the final determined causality assessment was completed.

After the case details were reviewed by Takeda, it was determined that the self-limited event of “allergic rhinitis” was not related to Adynovi and was consistent with environmentally mediated allergies.

In addition, Takeda conducted a full cumulative search in the Takeda Global Safety Database, from 21 July 2011 (Development International Birth Date), to 30 August 2024, for the Preferred Term (PT) of “Rhinitis” and PT of “Allergic Rhinitis,” under System Organ Classes (SOC) of “Respiratory, thoracic and mediastinal disorders,” and SOC “Infections and infestations.”

The cumulative search yielded 4 cases (2 from South Korea, one of which was from study 261603 [both reported in 2023]; 1 from Brazil [2022]; and 1 from Germany [2021]). All the events were nonserious, self-limited and consistent with upper respiratory infections or seasonal allergies. Three of the events occurred in children (6, 7, and 12 years old) and age was not reported in the fourth case.

All cases were evaluated and determined to be unlikely to be related to Adynovi. Hence, based on this assessment, the benefit-risk profile of Adynovi remains positive, and it was determined that an update to the PI was not necessary at this time.

Assessment of Response

According to the Applicant the reported case of allergic rhinitis was initially classified as "unassessible/unclassifiable". To comply with local regulations based on the World Health Organization’s causality assessment the case was recorded as "related" before the final determined causality assessment was completed. However, after further review determined that the allergic rhinitis was self-limited and not related to Adynovi, aligning with environmentally mediated allergies.

A comprehensive search of Takeda's Global Safety Database from July 21, 2011, to August 30, 2024, identified four nonserious cases of rhinitis (two from South Korea, one from Brazil, and one from Germany). All events were consistent with upper respiratory infections or seasonal allergies, predominantly in children (3/4) and unlikely related to Adynovi, which is agreed.

Conclusion:

Issue resolved and no update of the PI is necessary.

4. Rapporteur’s overall conclusion and recommendation

☒ Fulfilled:

No regulatory action required.