19 June 2025
EMADOC-1700519818-2272682
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: EMA/PAM/0000245372

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
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Status of this report and steps taken for the assessment				
Current step	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Start of procedure	27 Jan 2025	27 Jan 2025	☐
☐	CHMP Rapporteur Assessment Report	3 March 2025	3 March 2025	☐
☐	CHMP members comments	17 March 2025	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	20 March 2025	n/a	☐
☐	CHMP adoption of Request for Supplementary information	27 March 2025	27 March 2025	☐
☐	Submission	20 May 2025	18 May 2025	☐
☐	Re-start	21 May 2025	21 May 2025	☐
☐	CHMP Rapporteur Assessment Report	04 Jun 2025	04 Jun 2025	☐
☐	CHMP members comments	10 Jun 2025	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	12 Jun 2025	n/a	☐
☒	CHMP adoption of conclusions:	19 Jun 2025	19 Jun 2025	☐

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1. Introduction

On 20 June 2024, the MAH submitted a completed paediatric study for Adynovate (authorised in the EU under the trade name 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 TAK-660-4010 (Taiwan) is a standalone study.

The study is not part of the PIP or the clinical development program of Adynovi.

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 factor VIII (FVIII) with an extended half-life. It belongs to the pharmacotherapeutic group of coagulation FVIII (Anatomical Therapeutic Chemical code: B02BD02).

In the EU, rurioctocog alfa pegol was authorized on 08 January 2018 (under the trade name Adynovi). Adynovi is approved for the treatment and prophylaxis of bleeding in patients 12 years and above with hemophilia A (congenital FVIII deficiency).

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- **Study TAK-660-4010;** a post-authorisation, prospective, multi-center, non-interventional study conducted to investigate the clinical benefits of ADYNOVATE® plus myPKFiT® for patients with severe hemophilia A, in accordance with Taiwan's reimbursement guidelines.

Survey period lasted from 13th December 2021 to the 14th of January 2023.

2.3.2. Clinical study

Study TAK-660-4010
The aim of this study was to assess the impact of pharmacokinetic (PK)-guided prophylaxis using extended half-life (EHL) recombinant factor VIII (rFVIII) on trough level, clinical outcome, daily activity level, and quality of life in patients with hemophilia A, referred to as ATTRACT-HA.

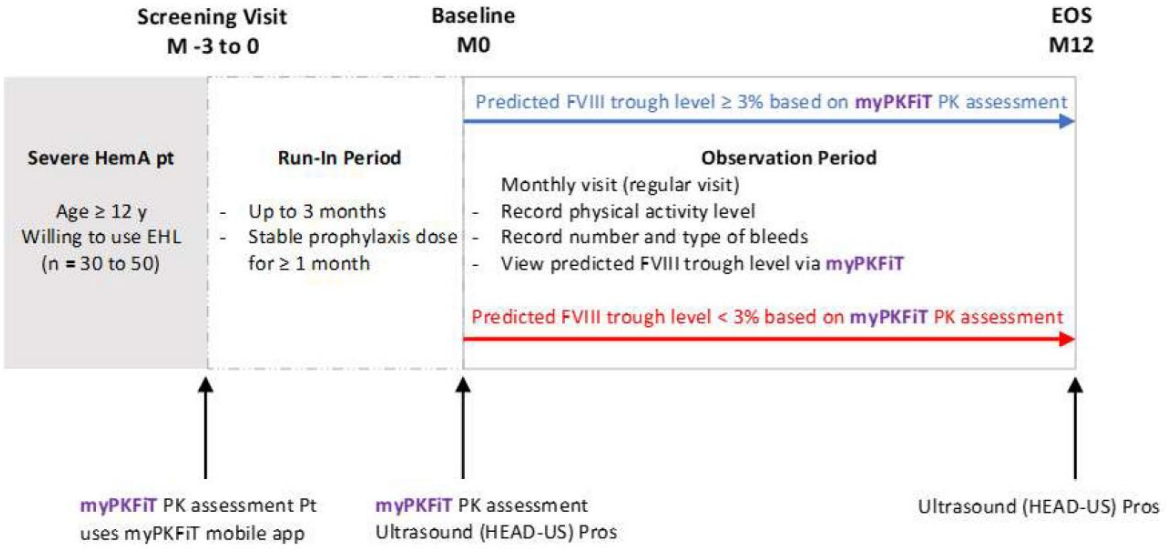
Description

Study TAK-660-4010 was a prospective, multicenter trial that assessed the effect of PK-guided prophylaxis of extended half-life rFVIII on trough level using myPKFiT, clinical outcome, daily activity level, and QoL in patients with hemophilia A (ATTRACT-HA trial). The purpose of the trial was to provide an answer as to whether Adynovate plus myPKFiT could improve clinical outcomes, increase

activity levels, and improve patient's QoL. Taiwan's reimbursement criteria for Adynovate specify a maximum of 50 IU/kg per infusion, given twice a week for primary prophylaxis.

myPKFiT is a medical device that has been approved in the EU, US, Japan, and Taiwan. It is made up of web and mobile applications. Authorized healthcare professionals can use the myPKFiT web application to simulate personalized dosing regimens of rFVIII drugs (ADVATE and ADYNOVATE). The application uses minimum patient-specific details for an adequate dose calculation of each drug. myPKFiT can predict how much medicine patients need to achieve treatment goals using a computer model based on patient information.

Figure 1: study schema



Methods

Study participants

Inclusion criteria:

1) A confirmed diagnosis of severe hemophilia A (FVIII clotting activity <1%)

2) The patient was ≥12 years old

3) The patient had a body weight of ≥ 30kg and ≤ 140 kg

4) The patient had historical bleeding data for 6 months prior to the screening visit.

5) Patients were receiving prophylactic treatment with ADYNOVATE, and had been on a stable dosing regimen for ≥ 1 month prior to the baseline visit

6) Patient was using myPKFiT for personalized prophylaxis at the baseline visit

7) The patient was receiving prophylactic treatment with ADYNOVATE® and had a predicted FVIII trough level of ≥1% at the baseline visit (myPKFit® predicted that the patient`s FVIII trough level would be ≥ 1 % for at least 80% of the time over one week based on the patient's PK parameters and prescribed dosing regimen at the baseline visit).

8) Patients provided informed consent, or their legal representative provided informed consent.

Exclusion criteria:

1) FVIII inhibitor-positive with a confirmed inhibitory antibody to FVIII with a titer of ≥ 0.6 Bethesda Units (BU) using the Nijmegen modification of the Bethesda assay

2) Patients with any condition or circumstance that, in the opinion of the investigator, would compromise the safety of the patient or the quality of the study data.

Treatments

This was a non-interventional study in which medicinal product(s)/medical device(s) were prescribed/used in the usual manner in accordance with the terms of the marketing authorization. Patients entered a 12-month observation period and continued using PK-guided prophylaxis with ADYNOVATE on the prescribed dosing regimen. Patients returned to the study site monthly during the observation period and completed the PRO assessments.

Objective(s)

The myPKFiT PK assessment at baseline determined whether the patient was in the FVIII trough level ≥ 3% group or FVIII trough level < 3% group. A patient was in the FVIII trough level ≥ 3% group if myPKFiT predicted the patient's FVIII trough levels to be ≥ 3% for at least 80% of the time over one week based on the patient's PK parameters and the prescribed dosing regimen.

Otherwise, the patient was in the FVIII trough level < 3% group. The time above the FVIII trough level 3% was recorded for each patient in the dosage calculation section of the myPKFiT® web application.

Primary Objective

To evaluate whether a predicted FVIII trough level of ≥ 3% can improve outcomes of patients with hemophilia A assessed by ABR and AJBR.

Secondary Objective(s)

To evaluate whether a predicted FVIII trough level of ≥ 3% can improve the clinical outcome of hemophilia A patients, as assessed by joint ultrasound [HEAD-US], and whether PK-guided prophylaxis can improve the clinical outcome of hemophilia A patients with a predicted FVIII trough level of< 3%, assessed by ABR, AJBR, and joint ultrasound [HEAD-US].

All Patients

To evaluate whether PK-guided prophylaxis can improve the clinical outcomes of patients with hemophilia A assessed by ABR, AJBR, and joint ultrasound [HEAD-US].

Exploratory Objective(s)

FVIII trough level ≥ 3%

- To evaluate whether predicted FVIII trough level of ≥ 3% affects the presence or absence of bleeds and joint bleeds
- To evaluate whether predicted FVIII trough level of ≥ 3% can increase the patient`s daily activity level
- To evaluate whether predicted FVIII trough level of ≥ 3% can improve patient quality of life

FVIII trough level < 3%

- To evaluate whether PK-guided prophylaxis affects the presence or absence of bleeds and joint bleeds in patients with a predicted FVIII trough level of< 3%
- To evaluate whether PK-guided prophylaxis can increase daily activity in patients with a predicted FVIII trough level of< 3%
- To evaluate whether PK-guided prophylaxis can improve daily quality of life in patients with a predicted FVIII trough level of< 3%

All Patients

- To evaluate whether PK-guided prophylaxis affects the presence or absence of bleeding and joint bleeding
- To evaluate whether PK-guided prophylaxis can increase patient daily activity level
- To evaluate whether PK-guided prophylaxis can improve patient daily quality of life

Outcomes/endpoints

Primary endpoints

Changes in ABR and AJBR at month 12 from the ABR and AJBR for the 6 months before screening in patients with a predicted FVIII trough level of ≥ 3%

Secondary endpoints

FVIII trough level ≥ 3%

- Change in the HEAD-US score assessed by joint US from month 0 to month 12 in patients with a predicted FVIII trough level of FVIII trough level < 3%
- Changes in ABR and AJBR at month 12 from the ABR and AJBR for the 6 months before screening in patients with a predicted FVIII trough level of< 3%
- Change in the HEAD-US score assessed by joint ultrasound from month 0 to month 12 in patients with a predicted FVIII trough level of< 3%

All Patients

- Changes in ABR and AJBR at month 12 from ABR and AJBR for the 6 months prior to screening
- Changes in the HEAD-US score assessed by joint ultrasound from month 0 to month 12

Sample size

A minimum of 35 to a maximum of 60 patients were planned for enrolment in this study, with an anticipated evaluable sample size of 30-50 individuals. This estimate is based on a projected dropout rate of 10% and a non-compliance rate of 10%. The final number of patients was contingent on the availability of eligible patients at the participating sites. The sample size was determined by the estimated eligible patient population in Taiwan and was not calculated using statistical power methods because the primary endpoint was not anticipated to yield statistically significant results. The primary endpoint was analysed using descriptive statistics without a formal hypothesis test.

Randomisation and blinding (masking)

Not applicable. Study TAK-660-4010 was a non-interventional study.

Statistical Methods

In general, the statistical analyses for study TAK-660-4010 were descriptive in nature only. Continuous variables were summarized using descriptive statistics including n, mean, standard deviation (SD), standard error of the mean, Q1, median, Q3, minimum, and maximum.

No inferential statistical hypothesis testing procedures were applied.

Results

Participant flow/Numbers analysed

A total of 16 subjects were screened across the three study sites. Of these, 7 subjects (43.8%) were enrolled at each of the two sites, while 2 subjects (12.5%) participated at another. Among the 7 subjects with FVIII trough level < 3% group, 6 (85.7%) were located at the MMH site and 1 (14.3%) at the TSGH site. From the total screened, 9 subjects were in the FVIII trough level ≥ 3% group, 6 (66.7%) were in the TSGH site, 2 (22.2%) were in the FEMH site, and 1 (11.1%) was in the MMH site.

Table 1: Number of subjects who were screened and FVIII trough levels at each site

Site	Screened Total (N=16) n (%)	FVIII trough level*	
		FVIII trough level <3% (N=7) n (%)	FVIII trough level ≥3% (N=9) n (%)
TSGH	7 (43.8)	1 (14.3)	6 (66.7)
MMH	7 (43.8)	6 (85.7)	1 (11.1)
FEMH	2 (12.5)	0 (0.0)	2 (22.2)

*FVIII trough level ≥ 3% or FVIII trough level < 3% criteria: A patient is in the FVIII trough level ≥ 3% group, if myPKFiT® predicts the patient's FVIII trough levels is ≥ 3% for at least 80% of the time over one week based on the patient's PK parameters and prescribed dosing regimen. Otherwise, the patient is in the FVIII trough level < 3% group.

Of the 16 participants enrolled, 15 (93.8%) participants completed the trial. One pediatric participant (1/2) withdrew consent and discontinued the trial.

Table 2: Summary of Subject Dispositions

		Total (N=16) n (%)
Enrolled		16 (100.0)
Completed the study	Yes	15 (93.8)
	No	1 (6.3)
Discontinued reason	Withdrawal of consent	1 (6.3)
	Investigator/Sponsor decides that the subject should be discontinued from the study	0 (0.0)
	Lost to follow-up	0 (0.0)
	Adverse events	0 (0.0)
	Non-compliance with the study requirements	0 (0.0)
	Violation of eligibility criteria or study procedures	0 (0.0)
	Other	0 (0.0)

Recruitment

A total of 16 subjects were screened across three study sites in Taiwan (TSGH, MMH, FEMH).

Initiation of the study was December 13th 2021. Completion on the 14th January 2023.

Baseline data

All participants were male and Asian.

Of the 16 participants, 9 were in the FVIII trough level ≥3% group and 7 were in the FVIII trough level <3% group. The median age was 43.0 years (range: 28.0-63.0 years) for the FVIII trough level ≥3% group and 23.0 years for the FVIII trough level <3% group. Of these, 2 were **pediatric** participants, both of whom were in the FVIII trough level <3% group. All participants were aged ≥12 years per inclusion criteria. All 16 participants had a VWF antigen level of >50% and an inhibitory antibody to FVIII titer <0.05 BU/mL at baseline visit.

Table 3: Summary of demographics

		FVIII trough level	
	Total (N=16)	FVIII trough level <3% (N=7)	FVIII trough level ≥3% (N=9)
Age (years)			
>30, n (%)	9 (56.25)	1 (14.29)	8 (88.89)
≤30, n (%)	7 (43.75)	6 (85.71)	1 (11.11)
Mean (SD)	35.4 (15.35)	22.9 (7.56)	45.1 (12.46)
Median	33.5	23.0	43.0
(Minimum, Maximum)	(14.0, 63.0)	(14.0, 34.0)	(28.0, 63.0)
Interquartile range (Q1, Q3)	(25.0, 48.0)	(15.0, 29.0)	(35.0, 55.0)
Sex, n (%)			
Male	16 (100.0)	7 (100.0)	9 (100.0)
Female	0 (0.0)	0 (0.0)	0 (0.0)
Race, n (%)			
Asian	16 (100.0)	7 (100.0)	9 (100.0)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Black or African American	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiians or other Pacific Islanders	0 (0.0)	0 (0.0)	0 (0.0)
White	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)
Height (cm)			
Mean (SD)	167.80 (9.45)	171.77 (8.42)	164.71 (9.47)
Median	166.70	173.90	163.00
(Minimum, Maximum)	(152.00, 182.50)	(161.00, 182.50)	(152.00, 182.00)
Interquartile range (Q1, Q3)	(162.00, 174.00)	(163.0, 181.00)	(161.00, 168.00)
Weight (kg)			
Mean (SD)	70.86 (13.48)	70.43 (15.51)	71.19 (12.65)
Median	68.95	70.30	65.00
(Minimum, Maximum)	(46.20, 89.90)	(46.20, 89.90)	(58.20, 89.00)
Interquartile range (Q1, Q3)	(60.85, 86.00)	(58.00, 88.00)	(61.70, 84.00)
BMI (kg/m^2)			
Mean (SD)	25.28 (5.28)	23.71 (4.01)	26.50 (6.04)
Median	23.20	23.20	23.20
(Minimum, Maximum)	(16.60, 37.90)	(16.60, 28.10)	(20.70, 37.90)
Interquartile range (Q1, Q3)	(22.10, 27.55)	(21.80, 27.00)	(22.30, 30.70)

Efficacy results

- Primary endpoint

Change in ABR and AJBR in participants with a predicted FVIII trough level ≥3%

Table 4a: change in ABR and AJBR between the 6 months prior screening and the 12-month observation period in the FVIII trough level ≥3 % group (full analysis set)

		ABR and AJBR in the FVIII trough level ≥3% group		
		6 months prior to screening	12-month observation period	p-value
ABR	N	9	9	
	Mean (SD)	2.89 (3.89)	2.44 (2.55)	-
	Median (Q1, Q3)	0.00 (0.00, 8.00)	2.00 (0.00, 5.00)	-
	(Min, Max)	(0.00, 8.00)	(0.00, 6.00)	-
	Change in ABR, Mean (SD)	-	-0.44 (3.81)	0.7355
AJBR	N	9	9	
	Mean (SD)	2.89 (3.89)	2.22 (2.49)	-
	Median (Q1, Q3)	0.00 (0.00, 8.00)	1.00 (0.00, 4.00)	-
	(Min, Max)	(0.00, 8.00)	(0.00, 6.00)	-
	Change in AJBR, Mean (SD)	-	-0.67 (3.64)	0.5977

Source: TAK-660-4010 CSR, Table 6.
p-values were derived using a paired t-test or a Wilcoxon signed rank test (if the normal assumption was violated).

- Secondary endpoints

Change in the HEAD-US score

Clinical outcomes of participants were assessed by joint ultrasound using the HEAD-US scoring system. The HEAD-US is a scanning and scoring method that evaluates joints (knees, elbows, and ankles) based on indicators of disease activity (synovitis) and structural damage (cartilage and bone) and provides a maximum score of 48 (a higher score represents lower joint health).

Table 4b: change in HEAD-US total score (0-48) assessed by joint ultrasound between month 0 and month 12 (full analysis set)

		HEAD-US total scores		
		Month 0	Month 12	p-value
FVIII trough level <3%	N	7	6	
	Mean (SD)	4.29 (3.55)	4.17 (4.02)	-
	Median (Q1, Q3)	4 (0, 6)	4 (0, 8)	-
	(Min, max)	(0, 10)	(0, 9)	-
	Change in HEAD-US scores, Mean (SD)	-	-0.17 (1.33)	0.7711
FVIII trough level ≥3%	N	9	9	
	Mean (SD)	24.11 (7.91)	25.44 (10.74)	-
	Median (Q1, Q3)	25 (21, 28)	26 (21, 31)	-
	(Min, max)	(8, 34)	(5, 40)	-
	Change in HEAD-US scores, Mean (SD)	-	1.33 (6.69)	0.5664
Total	N	16	15	
	Mean (SD)	15.44 (11.90)	16.93 (13.71)	-
	Median (Q1, Q3)	14 (5, 25)	17 (5, 28)	-
	(Min, Max)	(0, 34)	(0, 40)	-
	Change in HEAD-US scores, Mean (SD)	-	0.73 (5.18)	0.5918

Source: TAK-660-4010 CSR, Table 7.
p-values were derived using a paired t-test or a Wilcoxon signed rank test (if the normal assumption was violated).

Change in ABR and AJBR in participants with a predicted FVIII trough level <3%

Table 4c. change in ABR and AJBR between the 6 months prior to screening and the 12-month observation period in the FVIII trough level <3% group (full analysis set)

		ABR and AJBR in the FVIII trough level <3% group		
		6 months prior to screening	12-month observation period	p-value
ABR	N	7	7	
	Mean (SD)	4.29 (5.82)	1.86 (2.12)	-
	Median (Q1, Q3)	2.00 (0.00, 8.00)	1.00 (0.00, 4.00)	-
	(Min, Max)	(0.00, 16.00)	(0.00, 5.00)	-
	Change in ABR, Mean (SD)	-	-2.43 (5.68)	0.3013
AJBR	N	7	7	
	Mean (SD)	4.00 (6.00)	1.71 (2.21)	-
	Median (Q1, Q3)	2.00 (0.00, 8.00)	0.00 (0.00, 4.00)	-
	(Min, Max)	(0.00, 16.00)	(0.00, 5.00)	-
	Change in AJBR, Mean (SD)		-2.29 (5.91)	0.6250

Source: TAK-660-4010 CSR, Table 8.
p-values were derived using a paired t-test or a Wilcoxon signed rank test (if the normal assumption was violated).

Of the 2 pediatric participants, 1 had 1 bleeding episode within 6 months prior to screening and no bleeding during the 12-month observation period. The other participant had 1 bleeding episode within 6 months prior to screening and 5 bleeding episodes during the observation period before discontinuing the trial.

- Exploratory endpoints

Change in the proportion of participants with ABR and AJBR of 0

Table 4d. change in the proportion of participants with ABR and AJBR of 0 between 6 months prior to screening and the 12-month observation period (full analysis set)

		Proportion of Participants With ABR and AJBR of 0		
		6 months prior to screening (N=16)	12-month observation period (N=16)	p-value
Proportion of participants with ABR of 0	FVIII trough level <3%, n (%)	2 (28.6)	3 (42.9)	0.3173
	FVIII trough level ≥3%, n (%)	5 (55.6)	4 (44.4)	0.5637
	Total, n (%)	7 (43.8)	7 (43.8)	1.0000
Proportion of participants with AJBR of 0	FVIII trough level <3%, n (%)	3 (42.9)	4 (57.1)	0.3173
	FVIII trough level ≥3%, n (%)	5 (55.6)	4 (44.4)	0.5637
	Total, n (%)	8 (50.0)	8 (50.0)	1.0000

Source: TAK-660-4010 CSR, Table 9.
p-values were derived using McNemar's test.

Of the 2 pediatric participants (FVIII trough level <3% group), none had an ABR of 0 during the 6 months prior to screening, and 1 had an ABR of 0 during the 12-month observation period.

Change in daily activity level assessed by IPAQ

The IPAQ-Short Form was used to measure physical activity over the past 7 days. It recorded activity at 4 intensity levels: walking, moderate-intensity activities, and vigorous-intensity activities.

Table 5: Total physical activity

Total physical activity (MET-minutes/week)			Month 0	Month 12	P-value[1]
Total physical activity	FVIII trough level <3%	n (%)	6 (85.7)	6 (85.7)	0.2500
		Mean (SD)	3786.00 (5007.10)	15845.25 (19674.16)	
		Median (Q1, Q3)	1386.00 (0.00, 8424.00)	7911.75 (0.00, 24560.00)	
		(Minimum, Maximum)	(0.00, 11520.00)	(0.00, 44688.00)	
	FVIII trough level ≥ 3%	n (%)	8 (88.9)	9 (100.0)	0.3750
		Mean (SD)	3363.06 (6978.31)	4659.33 (10694.08)	
		Median (Q1, Q3)	663.50 (399.00, 2169.75)	1386.00 (240.00, 2430.00)	
		(Minimum, Maximum)	(0.00, 20440.00)	(0.00, 33048.00)	
	Total	n (%)	14 (87.5)	15 (93.8)	0.0488
		Mean (SD)	3544.32 (5992.60)	9133.70 (15354.66)	
		Median (Q1, Q3)	663.50 (0.00, 3372.00)	1386.00 (0.00, 15823.50)	
		(Minimum, Maximum)	(0.00, 20440.00)	(0.00, 44688.00)	

Of the 2 pediatric participants in the FVIII trough level <3% group, 1 did not have Month 12 data because of early discontinuation.

Change in QoL and activity capability assessed by Haem-A-QoL/Haemo-QoL and HAL/PedHAL

Table 6: change in quality of life between month 0 and month 12 assessed by Haem-A-QoL questionnaire

Quality of life score			Month 0	Month 12	P-value[1]
All age groups	FVIII trough level <3%	N (%)	7 (43.8)	6 (37.5)	0.1086
		Mean (SD)	30.46 (14.81)	40.37 (17.46)	
		Median (Q1, Q3)	27.02 (16.67, 47.28)	43.92 (31.59, 54.35)	
		(Minimum, Maximum)	(11.33, 51.11)	(11.90, 56.52)	
	FVIII trough level ≥3%	n (%)	9 (56.3)	9 (56.3)	0.2151
		Mean (SD)	39.27 (12.95)	33.15 (11.42)	
		Median (Q1, Q3)	42.93 (28.89, 48.37)	30.92 (26.09, 38.04)	
		(Minimum, Maximum)	(18.89, 55.00)	(20.11, 58.15)	
	Total	n (%)	16 (100.0)	15 (93.8)	0.7766
		Mean (SD)	35.42 (14.06)	36.03 (14.03)	
		Median (Q1, Q3)	34.79 (25.00, 47.83)	34.78 (26.09, 52.72)	
		(Minimum, Maximum)	(11.33, 55.00)	(11.90, 58.15)	

Raw scores are transferred scale score between 0 and 100 in which higher values represent a lower quality of life.

[1]P-value derived by paired *t*-test or Wilcoxon signed rank test (if the normal assumption is violated)

The mean PedHAL score for the pediatric participants (FVIII trough level <3%) was 99.25 (1.07) at Month 0. Of the 2 pediatric participants, 1 did not have Month 12 PedHAL data because of early discontinuation; the other pediatric participant had a PedHAL score of 83.40 at Month 12.

Safety results

Of the 16 participants enrolled, 10 (62.5%) participants experienced a total of 21 AEs. Most AEs (66.7%) were of mild severity and there were no severe or life-threatening AEs. There were no deaths and no SAEs, and all 21 AEs were unrelated to trial treatment.

Table 7a summary of Aes (full analysis set)

		Total (N=16)
Number of participants with a least 1 AE, n (%)		10 (62.5)
Number of AEs	n	21
AE severity/grade, n (%)	Mild	14 (66.67)
	Moderate	7 (33.33)
	Severe	0 (0.00)
	Life-threatening	0 (0.00)
	Death	0 (0.00)
SAE, n (%)	Yes	0 (0.00)
	No	21 (100.0)
Relationship to trial treatment, n (%)	Highly probable	0 (0.00)
	Probable	0 (0.00)
	Possible	0 (0.00)
	Unlikely	0 (0.00)
	Unrelated	21 (100.0)

Source: TAK-660-4010 CSR, Table 12.

Table 7b: AE by SOC and PT (full analysis set)

SOC PT	Total (N=16) n (%)
Number of participants with a least 1 AE	10 (62.5)
Infections and infestations	5 (31.25)
COVID-19	3 (18.75)
Cellulitis	1 (6.25)
Gingivitis	1 (6.25)
Musculoskeletal and connective tissue disorders	5 (31.25)
Haemarthrosis	4 (25.00)
Arthralgia	1 (6.25)
Pain in extremity	1 (6.25)
Gastrointestinal disorders	1 (6.25)
Gastroesophageal reflux disease	1 (6.25)
General disorders and administration site conditions	1 (6.25)
Peripheral swelling	1 (6.25)

Source: TAK-660-4010 CSR, Table 13.
AEs were coded using Medical Dictionary for Regulatory Activities Version 27.0.

Of the 2 pediatric participants, 1 experienced a total of 4 mild AEs of haemarthrosis. All 4 AEs were nonserious and unrelated to trial treatment.

2.3.3. Discussion on clinical aspects

In accordance with article 46 of regulation (EC) No 1901/2006, the MAH submitted the final report of study TAK-660-4010 with an updated Critical Expert Overview. Study TAK-660-4010 was a prospective, multi-center study in Taiwan to assess the effect of PK-guided prophylaxis with Adynovate plus myPKFiT of extended half-life (EHL) recombinant factor VIII (rFVIII) on trough level, clinical outcome, daily activity level and quality of life in patients with Hemophilia A (ATTRACT-HA).

Clinical outcomes were evaluated based on ABR and AJBR changes at month 12 compared to the 6 months before screening (based on historical data) and changes in HEAD-US score from month 0 to month 12. Additionally, changes in daily activity level and QoL (IPAQ, Haem-A-QoL/Haemo-QoL, and HAL/PedHAL) were evaluated based on PRO assessments at month 12 compared to baseline.

The study involved only 16 patients with severe hemophilia A, including **2 paediatric patients**. One patient had 1 bleeding episode within the 6 months prior to screening and experienced no bleedings during the 12-month observation period. The other patient had 1 bleeding episode within the 6 months prior to screening and experienced 5 bleeding episodes during the observation period before discontinuing the study. The small sample size severely limits the interpretability of the results. Upon request, missing listings referred to in the COA were submitted. Additionally, narratives for the 2 pediatric patients were presented. No concerns arise from the additional provided data in paediatric patients.

For the primary endpoint, numerical differences in ABR and AJBR were reported between the 12-month observation period compared to the 6 months before screening in participants with an FVIII trough level ≥3%.

Also for participants in the FVIII trough level <3% group (evaluated as a secondary endpoint) numerical differences in mean ABR and AJBR were reported during the 12-month period compared to the 6 months prior to screening. Due to the very limited sample size and also taking into account the comparison to historical data, clear limitations regarding possible conclusions are noted, hampering interpretability of these results.

Joint health, as measured by ultrasound using the HEAD-US scoring system, seemed to remain stable for both the FVIII trough level ≥3% and <3% groups throughout the observation period.

No treatment related AEs have been reported. No new safety signals were detected.

3. CHMP overall conclusion and recommendation

The inclusion of only two paediatric patients limits the interpretability of the reported results. From the available data, no new safety signals were observed in the paediatric population and no changes to the B/R balance of Adynovi were evident.

No updates to the PI are deemed necessary based on the provided new data.

☒ **Fulfilled**:

4. Request for supplementary information

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

1. The MAH is asked to provide the listings referred to in the COA as well as narratives for the 2 paediatric patients.

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

5. Evaluation of the MAH responses to the Request for supplementary information (RSI)

Question 1:

The MAH is asked to provide the listings referred to in the COA as well as narratives for the 2 paediatric patients.

MAH response:

To address the Agency's request for supplementary information, Takeda is submitting the listings as well as the narratives for the paediatric patients.

Assessment of MAH responses to Request for supplementary information

The MAH submitted the requested listings as well as the narratives for the paediatric patients. No concerns arise from presented data and the issue is considered resolved.