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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/0000258131

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

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Status of this report and steps taken for the assessment			
Current step	Description	Planned date	Actual Date
☐	CHMP Rapporteur AR	28 April 2025	28 April 2025
☐	CHMP comments	12 May 2025	N/A
☐	Updated CHMP Rapporteur AR	15 May 2025	N/A
☐	Request for Supplementary Information	22 May 2025	22 May 2025
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☐	Re-start date	25 June 2025	25 June 2025
☐	CHMP Rapporteur AR	09 July 2025	08 July 2025
☐	CHMP comments	14 July 2025	N/A
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1. Introduction

On 5 March 2025, the MAH submitted a completed study including paediatric participants aged ≥ 12 to < 18 years of age for Adynovate (authorised in the EU under the trade name Adynovi), in accordance with Article 46 of Regulation (EC) No 1901/2006, 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-660-3001 (China) 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-660-3001; a post-authorisation, phase 3, prospective, multicenter, open-label study of efficacy, safety, and pharmacokinetics of Adynovate administered for prophylaxis and treatment of bleeding in Chinese previously treated patients with severe hemophilia A (FVIII $< 1\%$)

The trial also aimed to provide Adynovate PK data in Chinese participants with severe hemophilia A.

Survey period lasted from 27th March 2023 to the 05th of September 2024.

2.3.2. Clinical studies

Study TAK-660-3001

The aim of this study was to assess the effectiveness and safety of Adynovate for preventing and treating bleeding episodes (BEs) in previously treated Chinese patients 12 to 65 years of age with severe hemophilia A (FVIII <1%). The trial also aimed to provide Adynovate PK data in Chinese participants with severe hemophilia A.

Description

Study TAK-660-3001 was a phase 3, post-authorization, multicenter, open-label trial evaluating Adynovate's efficacy for prophylaxis (based on annualized bleed rate), treatment of nonsurgical breakthrough bleeds, and perioperative bleeding control. The study also assessed safety, immunogenicity, pharmacokinetics (PK), health-related quality of life, and healthcare resource use (HRU), including hospitalizations.

It was planned to enroll at least 30 evaluable Chinese participants aged 12 to 65 years. All participants and/or legal representatives were required to provide signed informed consent. For screening, participants needed to undergo a minimum washout period of at least 72 to 96 hours following their last FVIII therapy (on-demand or prophylactic), if applicable. Thereafter, the trial screening procedures were performed for eligibility determination and were completed within 30 days prior to the initial PK assessment (if applicable) or baseline visit.

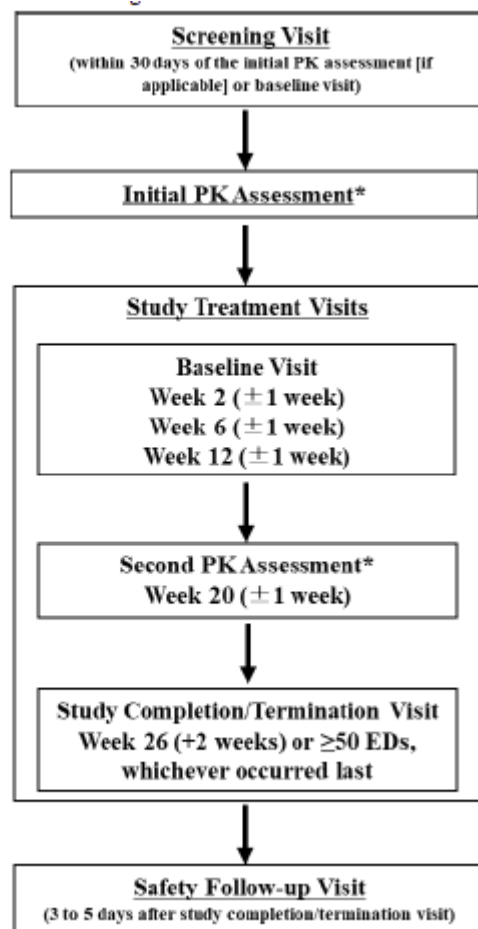
Screening procedures included demographics, medical/medication history, concomitant medications, AEs, physical examination, vital signs, and clinical laboratory assessments. Medical history (including immunization history) included surgery history, hemophilia history, BE history, and history of FVIII usage over the last year. Target joints and participants' ABR based on the previous 9 to 12 months were also recorded. Medication history included the name of the product, dose, dosing interval, and regimen start and end date.

It was planned for all enrolled participants to receive twice-weekly prophylactic treatment with Adynovate (45 ± 5 IU/kg) over a period of 26 weeks (+2 weeks) or at least 50 EDs, whichever occurred last.

PK evaluation following single dose and multiple doses of Adynovate was planned to be performed in at least 12 evaluable participants. For participants in the PK portion of the trial, the initial PK assessment was performed after a washout period of at least 72 to 96 hours following their last FVIII therapy (if applicable) and prior to the baseline visit. The second PK assessment was performed during the Week 20 (± 1 week) visit following the scheduled prophylactic treatment dose. The PK samples were collected at specified time points and measured for FVIII activity by a 1-stage clotting assay. For participants not in the PK portion, the baseline visit was initiated immediately upon eligibility confirmation.

Following the baseline visit, participants returned to the trial site for trial treatment visits at the following timepoints for the efficacy and safety assessments: Week 2 (± 1 week). Week 6 (± 1 week). Week 12 (± 1 week). Week 20 (± 1 week) (only for participants undergoing PK assessment), Trial Completion/Termination Visit: Week 26 (+2 weeks) or at least 50 EDs (whichever occurred last).

Figure 1: Trial schematic diagram



Methods

Study participants

Inclusion Criteria:

1. Participant and/or legally authorized representative must have voluntarily signed a written ICF after all relevant aspects of the trial had been explained and discussed with the participant. For the participants <18 years old, participants must have given assent AND their parents/legally authorized representative must have signed the ICF accordingly.
2. Participant and/or legally authorized representative understood and was willing and able to comply with all requirements of the trial protocol.
3. Participant should have been ethnic Chinese.
4. Participant was 12 to 65 years of age at screening and male.
5. Participant had severe hemophilia A (FVIII clotting activity <1%) as confirmed by the central laboratory at screening after a washout period of at least 72 to 96 hours.

6. The last on-demand or prophylactic treatment received was within 3 months before screening.
7. Participant had documented previous treatment with plasma-derived FVIII concentrates or recombinant FVIII for >150 EDs.
8. Participant was HIV-negative, or HIV-positive with stable disease and CD4+ count ≥ 200 cells/mm³.
9. Participant was HCV negative by antibody testing (if positive, additional polymerase chain reaction testing would be performed to confirm), as confirmed at screening; or HCV-positive with chronic stable hepatitis, as assessed by the investigator.

Exclusion Criteria:

1. Participant had detectable FVIII inhibitory antibodies (≥ 0.6 BU/mL using the Nijmegen modification of the Bethesda assay) as confirmed by the central laboratory at screening.
2. Participant had a confirmed history of FVIII inhibitory antibodies (≥ 0.6 BU using the Nijmegen modification of the Bethesda assay or ≥ 0.6 BU using the Bethesda assay) at any time prior to screening.
3. Participant had a known hypersensitivity to Adynovate or Advate or any of the components of the trial interventions, such as mouse or hamster proteins, or other FVIII products.
4. Participant had been diagnosed with an inherited or acquired hemostatic defect other than hemophilia A (for example, qualitative platelet defect or von Willebrand's disease).
5. Participant had severe hepatic dysfunction (for example, ≥ 5 times the ULN for ALT or AST, a recent or persistent INR >1.5 , as confirmed by the local laboratory at screening).
6. Participant had severe renal impairment (serum creatinine >1.5 times the ULN) as confirmed by the local laboratory at screening.
7. Participant was planned or likely to undergo major surgery during the trial period.
8. Participant had current or recent (<30 days) use of other PEGylated drugs before trial participation or scheduled use of such drugs during trial participation.
9. Participant had received emicizumab therapy within 6 months of screening.
10. Participant was currently receiving, or scheduled to receive during the trial, an immunomodulating drug (for example, systemic corticosteroid agent at a dose equivalent to hydrocortisone >10 mg/day, or α -interferon) other than antiretroviral chemotherapy.
11. Participant had participated in another clinical trial involving the use of an IP other than Adynovate or an investigational device within 30 days before the screening visit or was scheduled to participate in another clinical trial involving an IP or investigational device during this trial.
12. Participant had a medical, psychiatric, or cognitive illness or recreational drug/alcohol use that, in the opinion of the investigator, would affect participant safety or compliance.
13. Participant, in the opinion of the investigator, was unable or unwilling to comply with the trial protocol.

Treatments

Patients received twice-weekly prophylactic treatment with Adynovate (45±5 IU/kg) over a period of 26 weeks (+2 weeks) or at least 50 EDs, whichever occurred last. Adynovate was given intravenously as a bolus infusion over a period of less than or equal to 5 minutes (maximum infusion rate, 10 mL/min).

Objective(s)

The primary objective of this trial was to assess the efficacy of Adynovate for prophylactic treatment in previously treated Chinese participants with severe hemophilia A based on the total ABR.

The secondary objectives were to assess the efficacy of Adynovate for prophylactic treatment based on ABR by bleeding site and cause, the overall hemostatic efficacy rating of Adynovate for treatment of nonsurgical breakthrough BEs, and the efficacy of Adynovate for perioperative bleeding management. Additionally, this trial evaluated the safety as assessed by AEs and SAEs as well as clinically significant findings in vital signs and clinical laboratory parameters, the safety, and the immunogenicity of Adynovate based on the incidence of FVIII inhibitory Ab and binding Ab to Adynovate. PK evaluation was also performed in Chinese participants.

The exploratory objective of this trial was to assess the effect of Adynovate on health-related quality of life and HRU.

Outcomes/endpoints

Objective	Endpoint(s)
Primary	
To assess the efficacy of Adynovate for prophylactic treatment in previously treated Chinese participants with severe hemophilia A based on the total annualized bleeding rate (ABR)	Total ABR
Secondary	
To assess the efficacy of Adynovate for prophylactic treatment based on ABR by bleeding site and cause	- Annualized bleeding rates based on bleeding site and cause - Number of infusions and weight-adjusted consumption of Adynovate per week and month during the prophylactic treatment period - Proportion of participants with zero bleeding episodes (BEs) during the trial

Objective	Endpoint(s)
	Time intervals between BEs
To assess the overall hemostatic efficacy rating of Adynovate for treatment of nonsurgical breakthrough BEs during the trial period	- Overall hemostatic efficacy rating at bleed resolution for treatment of breakthrough BEs - Number of infusions and weight-adjusted consumption of Adynovate per BE
To assess the efficacy of Adynovate for perioperative bleeding management if minor surgery is performed during the trial period	- Overall assessment of hemostatic efficacy based on the Global Hemostatic Efficacy Assessment (GHEA) score as assessed by the operating surgeon/investigator - Intra- and postoperative actual versus predicted blood loss after the surgery, at postoperative day 1, and at discharge as assessed by the operating surgeon/investigator - Perioperative transfusion requirement of blood, red blood cells, platelets, and other blood products - Daily intra- and postoperative weight-adjusted consumption dose of Adynovate
To evaluate the safety of Adynovate as assessed by adverse events (AEs) and serious adverse events (SAEs) as well as clinically significant findings in vital signs and clinical laboratory parameters	- Occurrence of AEs and SAEs, total incidence, by severity, and by causality - Occurrence of thromboembolic events and hypersensitivity reactions - Clinically significant changes in vital signs and clinical laboratory parameters
To evaluate the safety and the immunogenicity of Adynovate based on the incidence of FVIII inhibitory antibodies and binding antibodies to Adynovate	- Immunogenicity: - Development of confirmed inhibitory antibodies (≥ 0.6 BU/mL using the Nijmegen modification of the Bethesda assay) to FVIII - Binding antibodies to Adynovate - Binding antibodies to Chinese hamster ovary (CHO) proteins
To evaluate the pharmacokinetic (PK) of Adynovate in Chinese participants	- Factor VIII activity (1-stage clotting assay) in PK samples collected for single-dose and steady-state PK assessments - Incremental recovery over time during prophylactic treatment at ED1 (exposure day 1), Week 6 (approximately ED10 to ED15), and ED50 - Predose FVIII (activity and antigen) and VWF (antigen) at scheduled visits - PK parameters including clearance (CL), volume of distribution (V), area under the concentration versus time curve between defined timepoints (AUC), C_{max}, $C_{predose}$, and elimination phase $T_{1/2}$, following a single dose and steady-state dosing, using noncompartmental analysis (NCA) methodology, subject to data availability

Exploratory Endpoints

- Health-related quality of life as assessed using the EQ-5D-5L.
- HRU endpoints, including number and duration of hospitalizations, number of emergency room visits, number of acute care visits, and number of days missed from school/work.

Sample size

At least 30 evaluable adult and adolescent participants (aged 12 to 65 years) were to be enrolled. The sample size was not based on statistical consideration. The evaluable participants were defined as all participants who were treated with Adynovate for a minimum of 50 EDs or approximately 26 weeks (+2 weeks), whichever occurred last. Participants who withdrew or discontinued before trial completion could be replaced.

Randomisation and blinding (masking)

There was no randomized allocation to trial intervention; all participants received the same prophylaxis dosing schedule of Adynovate.

Statistical Methods

There was no formal statistical hypothesis for this single arm open-label study.

The SAP was finalized prior to database lock. No interim analysis, adaptive design, or data monitoring committee was planned for this study.

Analysis Sets

The safety analysis set (SA set) comprised all participants treated with at least 1 Adynovate dose. All safety analyses were performed on the SA set.

The full analysis set (FAS) comprised all participants who were assigned to receive a treatment regimen of Adynovate. All efficacy analyses were performed on the FAS.

The per protocol analysis set (PPAS) comprised all participants who were treated with the prophylaxis Adynovate treatment regimen and complied with their originally assigned dose for the duration of trial participation. The participants who did not comply with the assigned doses were captured in the protocol deviation log, which was reviewed and finalized before the database lock. The PPAS was the supportive analysis set.

The PK full analysis set (PK FAS) comprised all participants who consented to PK evaluation, were treated with at least 1 Adynovate dose, and had at least 1 evaluable PK concentration postdose. All PK analyses were performed on the PK FAS.

The PK analysis set (PK AS), a subset of the PK FAS, comprised all PK participants who received at least 1 Adynovate PK dose with a sufficient number of evaluable PK concentrations postdose for the estimation of PK parameters using an NCA.

Results

Participant flow/Numbers analysed

A total of 41 participants were screened, of whom 4 (9.8%) were screen failures. Of the 37 participants who received at least 1 Adynovate dose, a total of 34 (91.9%) participants completed the trial intervention. Three (8.1%) participants discontinued the trial intervention. The reasons for discontinuing the trial were withdrawal by participant (2 [5.4%] participants) and other (1 [2.7%] participant).

Table 1: Overall participant disposition for the screened set

	n (%)
Signed ICF ^a	41 (100)
Screen Failures	4 (9.8)
Enrolled but not Treated	0
Received at Least 1 Adynovate Dose ^b	37 (100)
Completed Study Treatment	34 (91.9)
Discontinued Study Treatment	3 (8.1)
Reason for Discontinuation of Study Treatment ^b	
Withdrawal by Participant	2 (5.4)
Other	1 (2.7)
Completed Study ^c	34 (91.9)
Discontinued Study	3 (8.1)
Reason for Discontinuation of Study ^c	
Withdrawal by Participant	2 (5.4)
Other	1 (2.7)

37 (100%) participants were included in the FAS, PPAS, and SA set. 15 (40.5%) participants were included in the PK FAS and PK AS.

Recruitment

This clinical trial was a multicenter trial planned to be conducted in 12 trial sites in China. Of these, 11 trial sites enrolled participants during the trial.

The first participant signed informed consent form on 27 Mar 2023, last participant's last contact was on 5 Sep 2024.

Baseline data

All participants were male and Asian (ethnic Chinese).

A total of 27 (73%) participants were adults aged >18 to ≤65 years and 10 (27%) participants were adolescents aged ≥12 to <18 years.

Overall, the mean (SD) age for participants included in this trial was 24.1 (8.15) years, and the median age was 24.0 years (range: 13-46 years).

Table 2: Demographic characteristics (FAS)

Characteristic Statistics	Adynovate (N=37)
Age (years) at Informed Consent *	
n	37
Mean (SD)	24.1 (8.15)
Median	24.0
Q1, Q3	17.0, 29.0
Min, max	13, 46
Age (years) at Informed Consent Categories [n (%)]	
12 - <18	10 (27.0)
≥18 - 65	27 (73.0)

Twenty-five (67.6%) participants reported no target joints at screening, where a target joint was defined as a single joint (ankles, knees, hips, or elbows) with ≥ 3 spontaneous BEs in any consecutive 6-month period; 16 of the of 27 (59.3%) adult participants and 9 of 10 (90.0%) adolescent participants reported no target joints at screening.

Overall, the mean (SD) and median (Q1, Q3) ABR at baseline were 10.9 (14.49) and 5.0 (3.0, 13.0). For the adult group, the mean (SD) and median (Q1, Q3) ABR at baseline were 13.4 (15.75) and 8.0 (3.0, 20.0). For the adolescent group the mean (SD) and median (Q1, Q3) ABR at baseline were 4.1 (7.29) and 2.0 (0.0, 4.0), where baseline was defined as the last observed value prior to taking the first dose of IP (based on dates or date/times), or on the same day on taking the first dose of IP (based on dates), unless otherwise specified.

Efficacy results

Primary endpoint

Clinical outcomes of participants were assessed by the total ABR. A summary of ABR during prophylactic treatment is presented in Table 4.a.

During the treatment period, the overall mean (SD) total ABR was 4.1 (13.61) and the overall median (Q1, Q3) total ABR was 0.0 (0.0, 3.7). For adult participants, the mean (SD) total ABR was 5.0 (15.83) and the median (Q1, Q3) total ABR was 0.0 (0.0, 3.7). For adolescent participants, the mean (SD) total ABR was 1.8 (2.86) and the median (Q1, Q3) total ABR was 0.0 (0.0, 1.9).

The point estimate for mean (95% CI) of total ABR during the treatment period was 2.7 (1.4, 5.2) (adult participants: 3.2 [1.4, 7.2]; adolescent participants: 1.8 [0.6, 5.2]).

Table 3: Summary and analysis of ABR in FAS

Parameter Statistics	Adynovate (N=37)		
	12 - <18 (n=10)	≥18 - 65 (n=27)	Total (n=37)
Total ABR *			
Mean (SD)	1.8 (2.86)	5.0 (15.83)	4.1 (13.61)
Median	0.0	0.0	0.0
Q1, Q3	0.0, 1.9	0.0, 3.7	0.0, 3.7
Min, Max	0, 8	0, 83	0, 83
Point Estimate for Mean	1.8	3.2	2.7
95% CI for Mean ^b	0.6, 5.2	1.4, 7.2	1.4, 5.2

There were 4 BEs that were mistakenly recorded by participants, as documented by investigators in medical notes.

Secondary Endpoints

Prophylactic Treatment

ABR Based on Bleeding Site and Cause

A summary of ABRs by bleeding site and cause during prophylactic treatment is presented in Table 11.j below. During the treatment period, the bleeding site with the higher ABR was joints, with a mean (SD) of 2.7 (8.35) compared to non-joint sites, which had a mean (SD) of 1.4 (5.48). The spontaneous BEs had a higher ABR, with a mean (SD) of 3.8 (13.65) compared to injury-related BEs, which had a mean (SD) of 0.3 (0.99). The median ABR was 0 for all bleeding sites and causes. BEs of unknown cause were considered as spontaneous BEs.

Table 4: Summary of ABR by bleeding site and cause in FAS

Category Subcategory Statistics	Adynovate (N=37)		
	12 - <18 (n=10)	≥18 – 65 (n=27)	Total (n=37)
Bleeding Site			
Joint			
Mean (SD)	1.4 (2.48)	3.2 (9.66)	2.7 (8.35)
Median	0.0	0.0	0.0
Q1, Q3	0.0, 1.9	0.0, 2.0	0.0, 2.0
Min, Max	0, 6	0, 50	0, 50
Non-Joint			
Mean (SD)	0.4 (0.81)	1.7 (6.39)	1.4 (5.48)
Median	0.0	0.0	0.0
Q1, Q3	0.0, 0.0	0.0, 0.0	0.0, 0.0
Min, Max	0, 2	0, 33	0, 33
Cause			
Spontaneous/Unknown			
Mean (SD)	1.2 (2.48)	4.8 (15.88)	3.8 (13.65)
Median	0.0	0.0	0.0
Q1, Q3	0.0, 1.9	0.0, 3.7	0.0, 2.0
Min, Max	0, 8	0, 83	0, 83
Injury			
Mean (SD)	0.6 (1.33)	0.2 (0.85)	0.3 (0.99)
Median	0.0	0.0	0.0
Q1, Q3	0.0, 0.0	0.0, 0.0	0.0, 0.0
Min, Max	0, 4	0, 4	0, 4
All (n)			
Mean (SD)	1.8 (2.86)	5.0 (15.83)	4.1 (13.61)
Median	0.0	0.0	0.0
Q1, Q3	0.0, 1.9	0.0, 3.7	0.0, 3.7
Min, Max	0, 8	0, 83	0, 83

Source: [Table 15.2.2.2](#)

Total ABR was defined as both treated and non-treated bleeding episodes occurred during the treatment period, calculated as, $ABR = \text{number of unique bleeds occurred during treatment period} / (\text{length of treatment period [days]} / 365.25)$.

A summary of BEs by bleeding site and cause during prophylactic treatment is presented in Table 11.k below. Overall, the most frequently reported bleeding site was joints (12 participants), with 26 (70.3%) BEs. The most frequently reported cause of bleeding was spontaneous BEs (14 participants), with 31 (83.8%) BEs.

Table 5: Summary of BEs by bleeding site and cause in FAS

Category Subcategory Statistics	Adynovate (N=37)		
	12 - <18 (n=10)	≥18 – 65 (n=27)	Total (n=37)
Bleeding Site			
Joint (n1; m [%])	3; 7 (77.8)	9; 19 (67.9)	12; 26 (70.3)
Mean (SD)	0.7 (1.25)	0.7 (1.20)	0.7 (1.20)
Median	0.0	0.0	0.0
Q1, Q3	0.0, 1.0	0.0, 1.0	0.0, 1.0
Min, Max	0, 3	0, 4	0, 4
Non-Joint (n1; m [%])	2; 2 (22.2)	6; 9 (32.1)	8; 11 (29.7)
Mean (SD)	0.2 (0.42)	0.3 (0.68)	0.3 (0.62)
Median	0.0	0.0	0.0
Q1, Q3	0.0, 0.0	0.0, 0.0	0.0, 0.0
Min, Max	0, 1	0, 2	0, 2
Cause			
Spontaneous/Unknown (n1; m [%])	3; 6 (66.7)	11; 25 (89.3)	14; 31 (83.8)
Mean (SD)	0.6 (1.26)	0.9 (1.47)	0.8 (1.40)
Median	0.0	0.0	0.0
Q1, Q3	0.0, 1.0	0.0, 1.0	0.0, 1.0
Min, Max	0, 4	0, 5	0, 5
Injury (n1; m [%])	2; 3 (33.3)	2; 3 (10.7)	4; 6 (16.2)
Mean (SD)	0.3 (0.67)	0.1 (0.42)	0.2 (0.50)
Median	0.0	0.0	0.0
Q1, Q3	0.0, 0.0	0.0, 0.0	0.0, 0.0
Min, Max	0, 2	0, 2	0, 2
All (m)			
Mean (SD)	0.9 (1.45)	1.0 (1.45)	1.0 (1.43)
Median	0.0	0.0	0.0
Q1, Q3	0.0, 1.0	0.0, 2.0	0.0, 1.0
Min, Max	0, 4	0, 5	0, 5

Source: [Table 15.2.2.1](#)

m: number of specific unique BEs; n: number of participants; n1: number of participants with specific BEs.

Percentages are calculated as number of specific BEs/ number of total BEs.

Number of Infusions and Weight-adjusted Consumption of Adynovate per Week and Month during the Prophylactic Treatment Period

Adynovate consumption for prophylactic treatment is summarized in Table 11.m. The mean (SD) and median (Q1, Q3) number of infusions administered for the prophylactic treatment were 2.003 (0.0563) and 2.025 (1.989, 2.027) per week, 8.711 (0.2447) and 8.807 (8.649, 8.815) per month, and 49.730 (11.7914) and 53.0 (52.0, 53.0) per participant, respectively.

The mean (SD) and median (Q1, Q3) values of Adynovate consumption were 6185.407 (1439.9569) IU and 6007.913 (5352.237, 7290.624) IU per week, 26,895.475 (6261.2410) IU and 26,123.691 (23,272.673, 31,701.197) IU per month, and 1,53,009.554 (51,044.4778) IU and 157,237.500 (127,663.500, 179,291.500) IU per participant, respectively.

The mean (SD) and median (Q1, Q3) weight-adjusted values of Adynovate consumption were 89.637 (3.6807) IU/kg and 89.469 (87.239, 91.419) IU/kg per week, 389.760 (16.0045) IU/kg and 389.030 (379.334, 397.509) IU/kg per month, and 2230.318 (542.9449) IU/kg and 2329.717 (2260.391, 2413.618) IU/kg per participant, respectively.

Table 6: Summary and analysis of Adynovate consumption for prophylactic treatment in FAS

Parameter Statistics	Adynovate (N=37)		
	Per Week	Per Month	Per Participant
Number of Infusions			
n	37	37	37
Mean (SD)	2.003 (0.0563)	8.711 (0.2447)	49.730 (11.7914)
Median	2.025	8.807	53.000
Q1, Q3	1.989, 2.027	8.649, 8.815	52.000, 53.000
Min, Max	1.83, 2.12	7.95, 9.20	3.00, 58.00
Consumption of Adynovate (IU)			
n	37	37	37
Mean (SD)	6185.407 (1439.9569)	26895.475 (6261.2410)	153009.554 (51044.4778)
Median	6007.913	26123.691	157237.500
Q1, Q3	5352.237, 7290.624	23272.673, 31701.197	127663.500, 179291.500
Min, Max	3836.48, 10371.38	16681.83, 45096.98	9169.50, 265211.00
Weight-Adjusted Consumption of Adynovate (IU/kg)			
n	37	37	37
Mean (SD)	89.637 (3.6807)	389.760 (16.0045)	2230.318 (542.9449)
Median	89.469	389.030	2329.717
Q1, Q3	87.239, 91.419	379.334, 397.509	2260.391, 2413.618
Min, Max	83.00, 101.35	360.92, 440.69	130.43, 2852.30

Source: Table 15.2.2.4

n: number of participants in FAS.

Proportion of Participants with Zero BEs During the Trial

Table 7: Summary of zero BEs in FAS

Table 11.n Summary of Zero BEs in FAS

Category Subcategory Statistics	Adynovate (N=37)		
	12 - <18 (N=10)	≥18 – 65 (N=27)	Total (N=37)
	n (%)	n (%)	n (%)
Participants with zero BEs	6 (60.0)	14 (51.9)	20 (54.1)

Source: [Table 15.2.2.6](#)

Percentages are based on all participants within that age group in the FAS.

Total ABR during the trial is categorized as 0, >0. Participants with zero BEs (as in total ABR category of 0) during the trial are presented.

Time Intervals Between Bes

Table 8: Summary and analysis of average time interval between BEs in FAS

Parameter Statistics	Adynovate (N=37)		
	12 - <18 (N=10)	≥18 – 65 (N=27)	Total (N=37)
Average Time Interval Between BEs (Days)			
n	2	7	9
Mean (SD)	53.750 (10.2530)	64.188 (35.0844)	61.869 (30.9437)
Median	53.750	65.667	61.000
Q1, Q3	46.500, 61.000	45.000, 98.500	45.750, 91.500
Min, Max	46.50, 61.00	4.40, 98.50	4.40, 98.50
Average Time Interval Between BEs (Months)			
n	2	7	9
Mean (SD)	1.766 (0.3369)	2.109 (1.1527)	2.033 (1.0166)
Median	1.766	2.157	2.004
Q1, Q3	1.528, 2.004	1.478, 3.236	1.503, 3.006
Min, Max	1.53, 2.00	0.14, 3.24	0.14, 3.24

Source: [Table 15.2.2.7](#)

n: number of participants with more than 1 BE.

Average time interval between BEs (Days) = Length of treatment period(days)/ Number of unique bleeds occurred during treatment period.

Average time interval between BEs (Months) = [Length of treatment period(days)/ Number of unique bleeds occurred during treatment period]*12/365.25.

Average time interval was computed for participants with more than 1 unique BE.

Overall Hemostatic Efficacy Rating at Bleed Resolution for Treatment of Breakthrough Bes

The overall hemostatic efficacy rating is summarized by severity in Table 11.p below. There were 7 (22.6%) treated BEs reported as “Excellent”, including 3 minor, 3 moderate, and 1 major BE. There were 14 (45.2%) treated BEs reported as “Good”, including 7 minor, 7 moderate, and no major BEs. There were 4 (12.9%) treated BEs reported as “Fair”, including 1 minor and 3 moderate BEs. Efficacy treatment ratings were “Missing” in 6 (19.4%) treated BEs including 3 each for minor and moderate BEs.

Of the 31 treated breakthrough BEs, 25 episodes with nonmissing rating had a known hemostatic efficacy rating at bleeding resolution; 7 (28.0%) treated BEs reported as “Excellent”, including 3 minor, 3 moderate, and 1 major BE. There were 14 (56.0%) treated BEs reported as “Good”, including 7 minor, 7 moderate, and no major BEs. There were 4 (16.0%) treated BEs reported as “Fair”, including 1 minor and 3 moderate BEs.

Table 9: Summary of haemostatic efficacy rating by severity of bleeding for treated breakthrough BEs in FAS

Parameter Category	Adynovate (N=37)			
	Minor m (%)	Moderate m (%)	Major m (%)	Total m (%)
Overall Hemostatic Efficacy Rating at Resolution of Breakthrough BE				
Excellent	3 (9.7)	3 (9.7)	1 (3.2)	7 (22.6)
Good	7 (22.6)	7 (22.6)	0	14 (45.2)
Fair	1 (3.2)	3 (9.7)	0	4 (12.9)
None	0	0	0	0
Missing ^a	3 (9.7)	3 (9.7)	0	6 (19.4)
Total	14 (45.2)	16 (51.6)	1 (3.2)	31 (100)
Overall Hemostatic Efficacy Rating at Resolution of Breakthrough BE (Sensitivity Analysis) ^b				
Excellent	3 (12.0)	3 (12.0)	1 (4.0)	7 (28.0)
Good	7 (28.0)	7 (28.0)	0	14 (56.0)
Fair	1 (4.0)	3 (12.0)	0	4 (16.0)
None	0	0	0	0
Total	11 (44.0)	13 (52.0)	1 (4.0)	25 (100)

Source: Table 15.2.2.8

m: Number of bleeding events in that category of efficacy rating.

Percentages of events are based on the total number of treated BEs.

If multiple bleed severity or efficacy rating assessments were assessed for 1 BE, then only worst assessment was counted.

^a. The number of unique BEs without any overall hemostatic efficacy rating at resolution of breakthrough BE.

^b. Percentages of events are based on the total number of treated BEs with non-missing overall hemostatic efficacy rating at resolution of breakthrough BE.

Number of Infusions and Weight-Adjusted Consumption of Adynovate per BE

For the 14 participants with treated BEs, the mean (SD) and median (Q1, Q3) number of infusions were 6.286 (8.8181) and 3.50 (1.0, 5.0) per participant, respectively. The mean (SD) and median (Q1, Q3) Adynovate consumption were 12,820.714 (18,143.9630) IU and 5311.0 (2,355.0, 7866.0) IU per participant, respectively. The mean (SD) and median (Q1, Q3) weight-adjusted consumption of Adynovate were 172.383 (237.4619) IU/kg and 84.447 (30.825, 155.672) IU/kg per participant, respectively.

For the 31 treated BEs, the mean (SD) and median (Q1, Q3) number of infusions were 2.839 (2.9337) and 1.0 (1.0, 4.0) per BE, respectively. The mean (SD) and median (Q1, Q3) of Adynovate consumption were 5778.484 (6892.5848) IU and 3084.0 (1585.0, 6000.0) IU per BE, respectively. The mean (SD) and median (Q1, Q3) and weight-adjusted consumption of Adynovate were 77.766 (81.7538) IU/kg and 43.375 (25.0, 90.331) IU/kg per BE, respectively.

Adynovate consumption for treated BEs by age group is summarized below:

12 to <18 years subgroup: For the 4 adolescent participants with treated BE per participant, the mean (SD) and median (Q1, Q3) number of infusions were 1.083 (0.1667) and 1.0 (1.0, 1.167), respectively; the mean (SD) and median (Q1, Q3) of Adynovate consumption were 2109.792 (915.1959) IU and 2078.333 (1476.250, 2743.333) IU, respectively; the mean (SD) and median (Q1, Q3) weight-adjusted consumption of Adynovate were 31.199 (9.7379) IU/kg and 32.790 (24.117, 38.282) IU/kg, respectively.

For the 9 treated BEs in adolescent participants, the mean (SD) and median (Q1, Q3) number of infusions were 1.222 (0.6667) and 1.0 (1.0, 1.0) per BE, respectively; the mean (SD) and median (Q1, Q3) of Adynovate consumption were 1955.000 (1406.8490) IU and 1585 (1290, 1920) IU per BE, respectively; the mean (SD) and median (Q1, Q3) weight-adjusted consumption of Adynovate were 30.628 (21.0035) IU/kg and 25 (22.241, 30) IU/kg per BE, respectively.

18 to 65 years subgroup: For the 10 adult participants with treated BE per participant, the mean (SD) and median (Q1, Q3) number of infusions were 2.967 (2.6826) and 1.83 (1.0, 5.0), respectively; the mean (SD) and median (Q1, Q3) of Adynovate consumption were 6856.103 (8048.9331) IU and 3196.667 (2164.0, 9697.200) IU, respectively; the mean (SD) and median (Q1, Q3) weight-adjusted consumption of Adynovate were 83.885 (77.6845) IU/kg and 49.936 (30.825, 137.940) IU/kg, respectively.

For the 22 treated BEs in adult participants, the mean (SD) and median (Q1, Q3) number of infusions were 3.50 (3.2477) and 2.0 (1.0, 4.0) per BE, respectively; the mean (SD) and median (Q1, Q3) of Adynovate consumption were 7342.636 (7634.5146) IU and 3942.0 (2095.0, 9670.0) IU per BE, respectively; the mean (SD) and median (Q1, Q3) weight-adjusted consumption of Adynovate were 97.049 (89.6562) IU/kg and 52.277 (30.185, 137.553) IU/kg per BE, respectively.

Table 10: Summary and analysis of weight-adjusted Adynovate consumption for treated BEs in FAS

Parameter Statistics	Adynovate (N=37)					
	12 - <18 (N=10)		≥18 - 65 (N=27)		Total (N=37)	
	Per BE ^a	Per Participant ^b	Per BE ^a	Per Participant ^b	Per BE ^a	Per participant ^b
Number of Infusions						
n	9	4	22	10	31	14
Mean (SD)	1.222 (0.6667)	1.083 (0.1667)	3.500 (3.2477)	2.967 (2.6826)	2.839 (2.9337)	6.286 (8.8181)
Median	1.000	1.000	2.000	1.833	1.000	3.500
Q1, Q3	1.000, 1.000	1.000, 1.167	1.000, 4.000	1.000, 5.000	1.000, 4.000	1.000, 5.000
Min, Max	1.00, 3.00	1.00, 1.33	1.00, 11.00	1.00, 8.00	1.00, 11.00	1.00, 28.00
Consumption of Adynovate (IU)						
n	9	4	22	10	31	14
Mean (SD)	1955.000 (1406.8490)	2109.792 (915.1959)	7342.636 (7634.5146)	6856.103 (8048.9331)	5778.484 (6892.5848)	12820.714 (18143.9630)
Median	1585.000	2078.333	3942.000	3196.667	3084.000	5311.000
Q1, Q3	1290.000, 1920.000	1476.250, 2743.333	2095.000, 9670.000	2164.000, 9697.200	1585.000, 6000.000	2355.000, 7866.000
Min, Max	489.00, 5125.00	1032.50, 3250.00	1061.00, 26506.00	1287.00, 26506.00	489.00, 26506.00	1287.00, 57134.00
Weight-Adjusted Consumption of Adynovate (IU/kg)						
n	9	4	22	10	31	14
Mean (SD)	30.628 (21.0035)	31.199 (9.7379)	97.049 (89.6562)	83.885 (77.6845)	77.766 (81.7538)	172.383 (237.4619)
Median	25.000	32.790	52.277	49.936	43.375	84.447
Q1, Q3	22.241, 30.000	24.117, 38.282	30.185, 137.553	30.825, 137.940	25.000, 90.331	30.825, 155.672
Min, Max	8.43, 81.74	18.23, 40.98	21.97, 303.87	23.83, 245.20	8.43, 303.87	23.83, 738.38

Source: Table 15.2.3.3 and Table 15.2.2.5

^a n: number of specific treated BE.

^b n: number of participants with any treated BE in FAS.

Exploratory Endpoints

Health-related Quality of Life as Assessed using the EQ-5D-5L

The EQ-5D-5L used an index score based on the following dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and European Quality visual analogue scale score.

Minimal changes were observed in the mean EQ-5D-5L scores between baseline and end of trial by using Hodges-Lehmann estimator.

HRU Endpoints

Participants were asked to record parameters of HRU (number and duration of hospitalizations, number of emergency room visits, number of acute care visits, and number of days missed from school/work). There were no emergency room visits due to trial participation or severe hemophilia during the trial. Furthermore, median resource utilization on each annualized rate measure was zero, indicating participants were well-managed and did not require significant HRU.

PK results

A total of 15 Chinese participants underwent intensive PK sampling following an initial single dose and Week 20 (± 1 week) exposure to Adynovate. Among them, 1 participant discontinued from the trial before Week 20. Adynovate PK parameters based on FVIII activity were calculated via NCA Analysis method, and the summary is provided in Table 11 below. Pre-infusion corrected FVIII concentrations were used based on the pre-infusion FVIII concentration at single dose and multiple doses.

Table 11: Summary and analysis of Adynovate PK parameters by visit in PK AS

Visit PK Parameters	Statistics	Adynovate Total (≥ 18 –65 years) (N=15)
Initial PK Assessment		
AUC ₀₋₇₂ (h*IU/dL)	n	15
	Mean (SD)	2269 (684)
	CV%	30.1
AUC ₀₋₉₆ (h*IU/dL)	n	15
	Mean (SD)	2348 (737)
	CV%	31.4
AUC _{0-inf} (h*IU/dL)	n	15
	Mean (SD)	2405 (784)
	CV%	32.6
CL ([dL/h]/kg)	n	15
	Mean (SD)	0.0206 (0.00629)
	CV%	30.6
C _{max} (IU/dL)	n	15
	Mean (SD)	113 (26.1)
	CV%	23.1
C _{predose} (IU/dL)	n	15
	Mean (SD)	0 (0)
	CV%	NA
IR (IU/dL)/(IU/kg)	n	15
	Mean (SD)	2.50 (0.579)
	CV%	23.1
t _{1/2} (h)	n	15
	Mean (SD)	16.0 (3.27)
	CV%	20.4
t _{max} (h)	n	15
	Median	0.55
	Min, Max	0.45, 1.75
V (dL/kg)	n	15
	Mean (SD)	0.458 (0.107)
	CV%	23.4

Second PK Assessment (Week 20)

AUC _{0-72,ss} (h*IU/dL)	n	14
	Mean (SD)	2466 (658)
	CV%	26.7%
AR _{AUC0-72} (ratio)	n	14
	Mean (SD)	1.11 (0.135)
	CV%	12.2%
AUC _{0-96,ss} (h*IU/dL)	n	14
	Mean (SD)	2582 (736)
	CV%	28.5
AR _{AUC0-96} (ratio)	n	14
	Mean (SD)	1.12 (0.145)
	CV%	12.9%
CL _{ss} ([dL/h]/kg)	n	14
	Mean (SD)	0.0192 (0.00594)
	CV%	30.9
C _{max,ss} (IU/dL)	n	14
	Mean (SD)	115 (20.0)
	CV%	17.5
AR _{Cmax} (ratio)	n	14
	Mean (SD)	1.03 (0.131)
	CV%	12.7%
C _{predose,ss} (IU/dL)	n	14
	Mean (SD)	0 (0)
	CV%	NA
IR _{ss} (IU/dL)/(IU/kg)	n	14
	Mean (SD)	2.52 (0.486)
	CV%	19.3
t _{1/2 ss} (h)	n	14
	Mean (SD)	18.5 (4.61)
	CV%	25.0
t _{max ss} (h)	n	14
	Median	0.68
	Min, Max	0.42, 2.18
V _{ss} (dL/kg)	n	14
	Mean (SD)	0.480 (0.0953)
	CV%	19.9

Source: Table 15.2.5.1

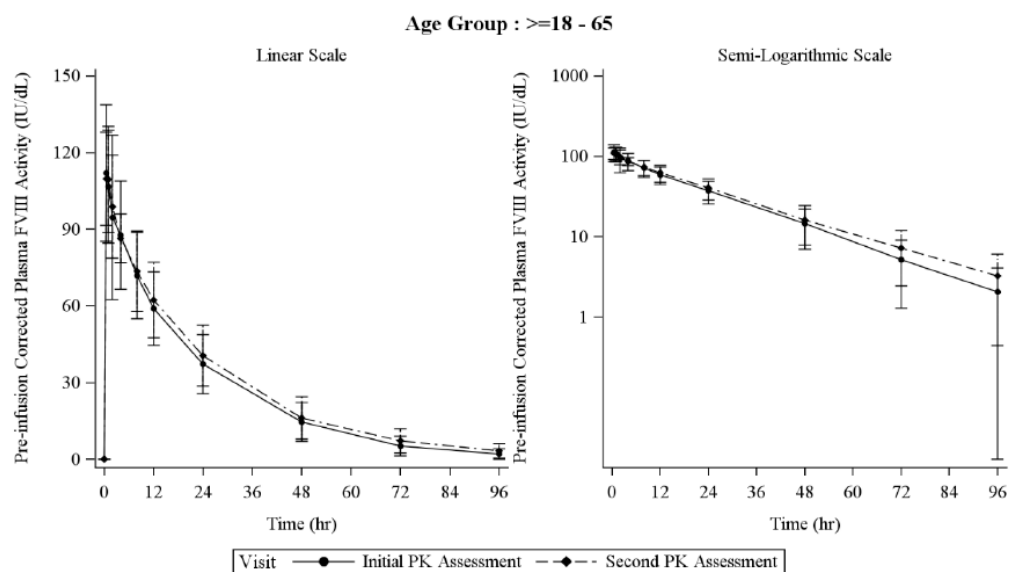
AR_{Cmax}: C_{max,ss}/C_{max}; AR_{AUC0-72}: AUC_{0-72,ss}/AUC₀₋₇₂; AR_{AUC0-96}: AUC_{0-96,ss}/AUC₀₋₉₆; IR: C_{max}/Dose.

Corrected PK parameters are calculated based on the corrected concentration data.

Geo. Mean: Geometric Mean, Geo. CV%: Geometric Coefficient of Variation, n: Number of Observations, N: Number of Participants, NA: Not Applicable.

Only corrected PK Parameters are included in the summary table.

Figure 2: Mean (+/- SD) Concentrations of FVIII activity over time in PK FAS



Source: [Figure 15.2.5.1](#)

Results with concentration between 0 to 1 were not displayed in the semi-logarithmic scale figure.

Following an initial 45 ± 5 IU/kg dose of Adynovate, the mean (SD) for AUC from time 0 to infinity and Cmax were 2405 (784) h*IU/dL and 113 (26.1) IU/dL, respectively, and the median (range) time to maximum concentration was 0.55 h (0.45 to 1.75 h). The mean (SD) for clearance and $t_{1/2}$ were 0.0206 (0.00629) (dL/h)/kg and 16.0 (3.27) h, respectively. Following the repeat dose PK assessment was performed at Week 20 (± 1 week) visit, the mean (SD) for CL and $t_{1/2}$ were 0.0192 (0.00594) (dL/h)/kg and 18.5 (4.61) h, respectively. The AUC and Cmax of repeat PK parameters were consistent with the initial parameters: ratio of AUC and Cmax was close to 1. Overall, results for the PK parameters (including AUC, Cmax, CL and $t_{1/2}$) were similar between the initial PK assessment and the second PK assessment, suggesting that Adynovate PK remained constant after repeat dosing.

IR during prophylactic treatment was assessed at baseline, Week 6, and end of trial. IR values in all age groups were approximately 2.5 and remained stable throughout the trial. Overall, the IR values were similar in the 2 age groups.

Table 12: Summary and analysis of IR for prophylactic treatment in SA set

Visit Statistics	Adynovate (N=37)		
	12 - <18 (N=10)	≥18 – 65 (N=27)	Total (N=37)
Baseline (ED1) ^a			
n	9	25	34
Mean (SD)	2.4247 (1.09105)	2.4968 (0.48503)	2.4777 (0.67876)
Median	2.1111	2.4667	2.4100
Q1, Q3	1.9267, 2.4044	2.2111, 2.6422	2.0489, 2.5978
Min, Max	1.662, 5.247	1.716, 3.871	1.662, 5.247
Week 6 (approximately ED10 to ED15)			
n	8	23	31
Mean (SD)	2.4192 (0.98724)	2.5480 (0.50059)	2.5147 (0.64379)
Median	2.2000	2.5333	2.4111
Q1, Q3	1.8233, 2.4444	2.1867, 2.8156	2.0289, 2.7933
Min, Max	1.676, 4.742	1.713, 3.536	1.676, 4.742
Trial Completion/Termination (ED50)			
n	10	21	31
Mean (SD)	2.4876 (0.67610)	2.3705 (0.41886)	2.4083 (0.50714)
Median	2.1811	2.4044	2.3578
Q1, Q3	2.0556, 2.8822	2.0400, 2.5578	2.0400, 2.5622
Min, Max	1.907, 3.893	1.698, 3.118	1.698, 3.893

Source: TAK-660-3001 CSR, Table 11.t.

Exposure day calculation started from the first PK infusion or baseline visit and completed at trial completion/termination visit. IR over the prophylactic treatments was calculated as $IR[(IU/dL)/(IU/kg)] = [PostFVIII (IU/dL) - PreFVIII (IU/dL)] / \text{Weight Adjusted Dose (IU/kg)}$.

^aBaseline was defined as the last observed value prior to taking the first dose of IP (based on dates or date/times), or on the same day on taking the first dose of IP (based on dates), unless otherwise specified. The IR determination at the baseline visit was only performed in participants who had not undergone PK assessment, while for PK participants the IR determination was done at the initial PK assessment.

Safety results

Extent of Exposure

A total of 37 participants were exposed to Adynovate during the trial. The mean (SD) and median (Q1, Q3) values for duration of prophylactic treatment were 173.9 (41.50) days and 183.0 (183.0, 187.0) days, respectively.

Three participants had <50 EDs and 34 participants had ≥50 EDs. The mean (SD) and median (Q1, Q3) total EDs of prophylactic treatment per participant were 49.7 (11.78) and 53.0 (52.0, 53.0) days, respectively. The mean (SD) and median (Q1, Q3) total EDs per participant were 52.5 (10.97) and 54.0 (53.0, 57.0) days, respectively. The mean (SD) and median (Q1, Q3) total consumption of Adynovate per participant were 2338.687 (511.5267) IU/kg and 2402.649 (2315.813, 2511.525) IU/kg, respectively, with

a mean (SD) total of 53.2 (10.60) infusions administered per participant. The mean (SD) and median (Q1, Q3) values for total consumption of Adynovate per participant for prophylaxis were 2230.318 (542.9449) IU/kg and 2329.717 (2260.391, 2413.618) IU/kg, respectively, with a mean (SD) total of 49.7 (11.79) prophylactic infusions per participant. The mean (SD) and median (Q1, Q3) values for total consumption of Adynovate per participant for treatment of BEs were 172.383 (237.4619) IU/kg and 84.447 (30.825, 155.672) IU/kg, respectively, with a mean (SD) total of 6.3 (8.82) infusions per participant to treat BEs.

Occurrence of AEs

Overall, 16 (43.2%) participants reported 48 TEAEs; 11 (40.7%) adult participants reported 41 TEAEs and 5 (50%) adolescent participants reported 7 TEAEs. Overall, the most frequently ($\geq 5\%$) reported TEAEs were arthralgia (7 events in 3 [8.1%] participants) and diarrhoea (3 events in 3 [8.1%] participants). In the adolescent group, the most frequently ($\geq 5\%$) reported TEAEs were platelet count increased, gastroenteritis, pericoronitis, palpitations, pyrexia, headache, and dermatitis (1 event each reported by 1 [10.0%] participant). Most TEAEs were mild in severity.

A total of 6 TEAEs were reported as treatment-related TEAEs; no treatment-related TEAEs were reported in the adolescent group.

Table 13: Treatment-related TEAEs by SOC and PT in SA Set

SOC PT	Adynovate (N=37)		
	12-<18 (N=10)	$\geq 18-65$ (N=27)	Total (N=37)
	n (%) m	n (%) m	n (%) m
Any treatment-related TEAE	0	3 (11.1) 6	3 (8.1) 6
Investigations	0	2 (7.4) 4	2 (5.4) 4
Alanine aminotransferase increased	0	2 (7.4) 2	2 (5.4) 2
Aspartate aminotransferase increased	0	2 (7.4) 2	2 (5.4) 2
Hepatobiliary disorders	0	1 (3.7) 1	1 (2.7) 1
Liver injury	0	1 (3.7) 1	1 (2.7) 1
Musculoskeletal and connective tissue disorders	0	1 (3.7) 1	1 (2.7) 1
Muscle spasms	0	1 (3.7) 1	1 (2.7) 1

Source: Table 15.3.1.6.

n: number of participants experiencing the event, m: number of events. m includes all events that occurred in each category.

Percentages are based on all participants within that age group in the SA set.

All AEs summarized here were those collected through EDC.

TEAEs were defined as any AEs emerging or manifesting at or after the initiation of the investigational product or any existing event that worsened in either intensity or frequency following exposure to the investigational product.

MedDRA dictionary version 27.0 was used.

AEs were classified into SOC and PT. Participants with 1 or more AEs within a level of MedDRA term are counted only once in that level.

1 SAE (preferred term: liver injury) was reported in 1 adult participant; this event was moderate and was considered treatment-related by the investigator but was assessed as unrelated by the sponsor due to pre-existing fatty liver disease and several concomitant medications with potential hepatotoxicity. No SAEs were reported in the adolescent group.

There were no TEAEs leading to IP withdrawal, no deaths, no severe TEAEs, no hypersensitivity reactions, no thromboembolic events, no anaphylactic reactions, and no severe hypersensitivity reactions reported during this trial.

Hematology

Overall, there were no trends observed in hematology parameters over the course of the trial.

Clinically significant findings were only observed in platelets for 3 participants (2 adults and 1 adolescent); a mild TEAE of platelet count increased was reported at Week 26 for 1 adolescent that was considered not related to the treatment by the investigator.

For all other parameters, there were no clinically significant findings at any time point.

Chemistry

Overall, there were no trends observed in chemistry parameters over the course of the trial.

Clinically significant findings were observed in some parameters at each time point.

A total of 13 adult participants had clinically significant chemistry values involving postinfusion aspartate aminotransferase, bilirubin, alanine aminotransferase, triglycerides, gamma-glutamyl transferase, cholesterol, and high-density lipoprotein and low-density lipoprotein cholesterol.

Most of these findings were present at both the pre- and postinfusion assessment at each time point. TEAEs in clinical chemistry parameters were reported for 5 participants.

No clinically significant findings were reported in the adolescent group.

Coagulation

None of the participants reported any clinically significant results in coagulation.

Vital Signs

Although changes in systolic and diastolic blood pressure were observed between pre- and postinfusion assessments for all participants across all time points, there were no trends observed over the course of the trial. 1 adult participant reported a clinically significant finding in pulse rate. There were no clinically significant findings in temperature or respiratory rate.

Immunogenicity

None of the participants tested positive for inhibitory Ab to FVIII, binding Ab (IgG, IgM) to Adynovate, or binding Ab to CHO proteins over the course of the trial.

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-660-3001 with an updated Critical Expert Overview. Study TAK-660-3001 was a prospective, multicentre, open-label phase 3 trial to evaluate the efficacy and safety of Adynovate (marketed in the EU as Adynovi) for prophylaxis and treatment of bleeding events in previously treated Chinese participants with severe haemophilia A, and to characterise Adynovate PK in Chinese HA patients. Eligible patients were previously treated Chinese HA patients with severe disease (FVIII <1%), 12 to 65 years of age. Participants were enrolled in 11 trial sites in China.

The primary objective of the study was the characterisation of Adynovate efficacy for prophylactic treatment based on total ABR, secondary objectives included assessment of efficacy based on ABR by bleeding site and cause, assessment of overall hemostatic efficacy rating of Adynovate for treatment of nonsurgical breakthrough bleeding events, evaluation of safety and immunogenicity, as well as evaluation of Adynovate PK in Chinese participants. Additionally, evaluation of health-related QoL and HRU were defined as exploratory objectives.

Clinical outcomes were evaluated based on total ABR (primary endpoint), as well as secondary endpoints including e.g. ABR based on bleeding site and cause, number of infusions and weight-adjusted consumption of Adynovate, proportion of zero bleeders, time intervals between bleeding events.

The overall study population comprised 37 participants (27 adults, 10 adolescents ≥ 12 to <18 years of age) who received at least 1 dose of Adynovate, of which 91.9% (34/37) completed the study treatment. 3 participants discontinued (2 due to withdrawal by participant, 1 due to other reasons not reported). Regarding analysis sets, all 37 participants were included in the FAS, PPAS, and SA set, 15 participants were included in the PK analysis sets.

At baseline, higher mean ABR was reported from the adult patient population, 13.4 (SD 15.75), compared to the adolescent group, 4.1 (SD 7.29). The MAH attributed the high mean baseline ABR reported from adult patients to local policies affecting the medical insurance coverage, stating that paediatric prophylaxis may be covered whereas coverage only included on demand treatment for adults.

Results from the PK evaluation were in line with previously available Adynovi data. No differences in Cmax were reported, as the the Cmax ratio (initial dose compared to repeat dose PK assessment at week 20) was 1.03 (SD 0.131). Slight increases in AUC0-72 and AUC0-96 were noted: ratio AUC0-72 1.11 (SD 0.135), ratio AUC0-96 1.12 (SD 0.145). Incremental recovery was consistent between age groups and time points.

For the primary endpoint, the overall mean (SD) total ABR was 4.1 (13.61). For adult participants the mean (SD) total ABR was 5.0 (15.83), and for adolescent participants the mean (SD) total ABR was 1.8 (2.86).

The proportion of zero bleeders during the study was comparable between age groups, with 6/10 (60%) reported from the adolescent subgroup and 27/37 (51.9%) reported from adults.

The hemostatic efficacy rating was "good" or "excellent" for the majority of breakthrough bleeding events.

For paediatric patients with treated bleeding events (n=4), the mean number of infusions was 1.083, while the respective mean number of infusions in adults (n=10) was higher (2.967), possibly due to

comparably worse bleeding control at baseline in these patients. Minimal changes in mean EQ-5D-5L scores between baseline and end of trial were reported, which are however considered to be of limited relevance given the open label single arm design of the study.

The reported efficacy data from Chinese HA patients are in line with previously available data from other clinical studies. Adynovi prophylactic treatment was efficacious across age groups.

TEAEs were reported from 40.7% (11/27) of adult participants and 50% (5/10) of adolescent participants. The most frequently reported TEAEs in the overall study population were arthralgia and diarrhoea. For adolescents, the reported TEAEs were platelet count increased, gastroenteritis, pericoronitis, palpitations, pyrexia, headache, and dermatitis (1 event each reported by 1 participant).

Overall, 6 related TEAEs were reported in 3 participants, none of whom were in the adolescent patient subgroup. The related TEAEs were ALAT increased and ASAT increased reported from 2 patients each, 1 case of liver injury (reported as SAE), and 1 case of muscle spasms. For all three participants, confounding factors were reported (i.e. pre-existing fatty liver disease and concomitant medication with known hepatotoxicity, history of hyperuricemia, history of elevated ALT levels and hyperuricemia), and the reported events either resolved or were in the process of resolving at the time of reporting. The MAH did not include these events in SmPC 4.8 as ADRs, which is acceptable given the confounding factors reported from patient narratives.

No deaths, no thromboembolic events, and no anaphylactic reactions were reported during the study. No inhibitors were detected in the study duration.

Overall, no concerns arise from the provided safety data.

Taken together, the provided results from study TAK-660-3001 in Chinese patients, including paediatric data, are in line with previously available data from other clinical trials. Adynovate/Adynovi was effective in the prophylactic treatment of severe haemophilia A patients and was well tolerated across age groups. Overall, no concerns arise from the provided data.

3. Rapporteur's overall conclusion and recommendation

☒ Fulfilled:

No regulatory action required.

4. Request for supplementary information

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

- The related TEAEs ALAT increased, ASAT increased, and muscle spasms reported from study TAK-660-3001 are currently not reflected in the EU Product information. The MAH is asked to justify their claim that no update to the SmPC section 4.8 is warranted.

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

MAH responses to Request for supplementary information

Question 1:

The related TEAEs ALAT increased, ASAT increased, and muscle spasms reported from study TAK-660-3001 are currently not reflected in the EU Product information. The MAH is asked to justify their claim that no update to the SmPC section 4.8 is warranted.

MAH responses

The MAH reviewed cases involving the 3 TAK-660-3001 participants who experienced increased levels of ALT, AST, or muscle spasms. Details of these cases are presented below.

Participant: a man, experienced moderate ALT and mild AST elevations. At the baseline visit in 2023 (Day 1), the participant received the first dose of Adynovate (46 IU/kg). The participant reported a moderate TEAE of ALT increased and 1 mild TEAE each of AST increased and weight increased. At Day 183, the participant reported an SAE of liver injury. The event was considered moderate. The participant was hospitalized due to subcutaneous bleeding in the left upper limb. Liver protection treatment was given during hospitalization. The trial intervention was discontinued on the same day.

No treatment was provided for the event. At Day 197, 15 days after trial intervention was discontinued, the event of liver injury resolved. The participant was discharged from the hospital on the same day. The events of ALT increased and AST increased resolved at Day 239 and at Day 295, respectively. At the time of database lock, the event of weight increased was ongoing.

The SAE of liver injury was considered by the investigator to be possibly related to Adynovate. The sponsor assessed the event as not related to trial intervention since the participant had a pre-existing condition of fatty liver disease diagnosed 2 years prior to enrollment into the trial with an upward trend in ALT observed during the screening interview. The participant had uneventfully received the trial intervention for 6 months and 2 days prior to the event of liver injury. However, in the few months prior to the liver injury, he received several concomitant drugs with known hepatotoxicity (sulindac, celecoxib, cefixime, and acetaminophen) that could have contributed to the event. After hospitalization, liver function showed improvement following the start of the liver protection regimen; however, it remains unclear whether this was due to the discontinuation of the trial intervention, the effectiveness of the liver protection regimen, or a combination of both. The SAE resolved, and the participant was discharged after 2 weeks. Given the underlying fatty liver and concomitant hepatotoxic medications, the level of evidence provided by this report is insufficient to directly implicate the trial intervention, and

the benefit-risk of the trial intervention remains positive. The sponsor would be continuing to monitor similar events according to company standard pharmacovigilance practices.

One participant had a history of hyperuricemia. The participant reported a mild event of muscle spasm. The reporting investigator classified the event of muscle spasm as related to the investigational product, while the MAH considered it unlikely to be related. The observed AE was likely confounded by the subject's underlying condition of hyperuricemia, with the intense pain and inflammation associated with this condition potentially causing muscle spasms as a protective mechanism (Comberg and Schach 2016; Zhang et al. 2025).

One participant experienced mild increases in ALT and AST. The participant had a history of elevated ALT levels and hyperuricemia. At screening, both ALT and AST levels were elevated, but only ALT was considered clinically significant. At baseline, both AST and ALT were within normal range, but eventually returned to elevated levels. Despite the high levels of both enzymes pre-baseline, the investigator still attributed these events to Adynovate treatment. However, the MAH assessed the events as unlikely related, instead suggesting that they were more likely connected to the subject's underlying medical history of hyperuricemia and history of elevated ALT levels. Research indicates that individuals with hyperuricemia often have elevated liver enzymes, implying a potential link between uric acid levels and liver function, which can contribute to liver inflammation and damage through various mechanisms (Lee *et al.* 2023).

Overall, a total of 37 participants were exposed to Adynovate during Trial TAK-660-3001. Among these, only 2 (5.4%) participants had elevated liver enzymes (ALT/AST), and 1 (2.7%) participant reported experiencing muscle spasms. It is important to note that all 3 participants had pre-existing liver conditions documented in their medical histories and all reported events were either resolved completely (recovered/ resolved) or were in the process of recovery (recovering/ resolving).

In summary, 2 of the 3 reviewed cases reported elevated ALT and/or elevated AST, and 1 case reported muscle spasms. All 3 had confounding factors with pre-existing related comorbidities. There was no compelling evidence of a causal relationship between these events and Adynovate treatment, therefore the SmPC does not require updating.

REFERENCES

- Comberg, H.-U. and Schach, S. 2016. Hyperuricemia is Associated with Musculo-skeletal Pain Results from a Cross-sectional Study. *The Open Pain Journal*, 9, 15-25.
- Lee, J. M., Kim, H. W., Heo, S. Y., Do, K. Y., Lee, J. D., Han, S. K., et al. 2023. Associations of Serum Uric Acid Level With Liver Enzymes, Nonalcoholic Fatty Liver Disease, and Liver Fibrosis in Korean Men and Women: A Cross-Sectional Study Using Nationally Representative Data. *J Korean Med Sci*, 38(34), e267.
- Zhang, J., Sun, N., Zhang, W., Yue, W., Qu, X., Li, Z., et al. 2025. The impact of uric acid on musculoskeletal diseases: clinical associations and underlying mechanisms. *Front Endocrinol (Lausanne)*, 16, 1515176.

Rapporteur's assessment:

The MAH submitted a summary of treatment-emergent adverse events (TEAEs) related to elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), and muscle spasms reported in study TAK-660-3001.

One participant developed a serious adverse event (SAE) of liver injury following elevations in liver enzymes and required hospitalization. The event resolved with treatment. Notably, the participant had a documented history of fatty liver disease diagnosed two years prior to study enrolment, with an upward trend in ALT already observed during screening.

A second participant experienced mild elevations in ALT and AST. This patient had a medical history of hyperuricemia and previously elevated ALT levels. At screening, both enzymes were elevated, although only ALT was deemed clinically significant.

The third participant reported a mild muscle spasm. Given the participant's history of hyperuricemia, the event was considered likely attributable to the underlying condition rather than the investigational product.

All three participants had pre-existing liver-related or metabolic conditions. The reported events either resolved or were in the process of resolving at the time of reporting. In light of these confounding factors, it is agreed that no update to the SmPC is required and the issue is considered resolved.