Amsterdam, 22 February 2024
EMA/106772/202423
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Advate

International non-proprietary name: Octocog alfa

Procedure no.: EMA/H/C/000520/P46/0102

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

Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	14 Aug 2023	14 Aug 2023	☐
☐	CHMP Rapporteur Assessment Report	18 Sep 2023	14 Sep 2023	☐
☐	CHMP members comments	02 Oct 2023	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	05 Oct 2023	n/a	☐
☐	Request for Supplementary Information	12 Oct 2023	12 Oct 2023	☐
☐	Submission	23 Jan 2024	23 Jan 2024	☐
☐	Re-start	24 Jan 2024	24 Jan 2024	☐
☐	CHMP Rapporteur Assessment Report	07 Feb 2024	07 Feb 2024	☐
☐	CHMP members comments	12 Feb 2024	12 Feb 2024	☐
☐	Updated CHMP Rapporteur Assessment Report	15 Feb 2024	n/a	☐
☒	CHMP adoption of conclusions:	22 Feb 2024	22 Feb 2024	☐

Declarations

☒ The assessor confirms that this assessment does **not** include non-public information, including commercially confidential information (e.g. ASMF, information shared by other competent authorities or organisations, reference to on-going assessments or development plans etc), irrespective from which entity was received*.

Table of contents

1. Introduction

On 2nd August 2023, the MAH submitted the results of the completed study (TAK-761-4009) for ADVATE that also involved paediatric patients, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

An addendum to the clinical overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study TAK-761-4009 is a stand-alone study. The study is not part of the PIP or the clinical development program of ADVATE.

2.2. Information on the pharmaceutical formulation used in the study

ADVATE is a third-generation recombinant FVIII concentrate, produced by a genetically engineered Chinese hamster ovary cell line and without the addition of any human or animal derived protein in the cell-culture process, purification, or final formulation. This production process virtually eliminates the risk of pathogen transmission. ADVATE is indicated for use in adults and children with hemophilia A for:

- Control and prevention of bleeding episodes
- Perioperative management
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes

ADVATE was first approved in the United States (US) on 25 July 2003 (= international birth date) for treatment of hemophilia A. In India, ADVATE was licensed in July 2015. ADVATE is currently licensed in 72 countries worldwide (as of June 2023) for the prevention and control of bleeding episodes and for perioperative management in patients with hemophilia A (congenital FVIII deficiency). ADVATE is not indicated for the treatment of von Willebrand's disease.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report(s) for:

- TAK-761-4009: A Phase 4, Multicenter, Prospective, Interventional, Post-Marketing Study in Hemophilia A Patients in India Receiving ADVATE as On-Demand or Prophylaxis Under Standard Clinical Practice.

The purpose of this study was to evaluate the safety and efficacy of ADVATE when used under standard clinical practice in previously treated hemophilia A subjects in India.

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

2.3.2. Clinical study

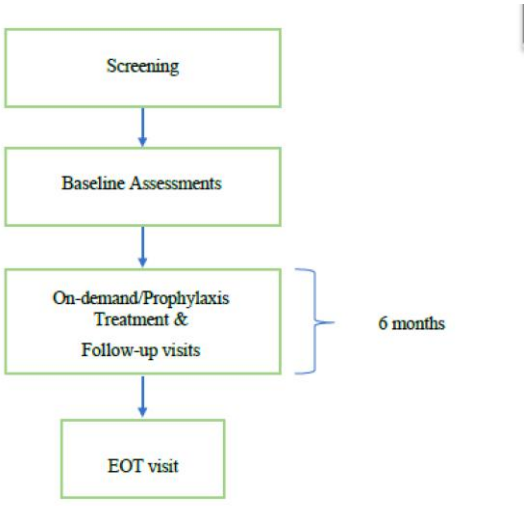
Clinical study number and title

TAK-761-4009: Phase 4, Multicenter, Prospective, Interventional, Post-Marketing Study in Hemophilia A Patients in India Receiving ADVATE as On-Demand or Prophylaxis Under Standard Clinical Practice

Description

This was a Phase 4, multicenter, prospective, interventional, single-group, post-marketing study in previously treated hemophilia A patients (PTPs) in India receiving ADVATE under standard clinical practice. Overall, 50 subjects belonging to any age group with hemophilia A were included in this study. All enrolled subjects who met the eligibility criteria were treated with ADVATE according to a dosing regimen determined by the treating physician and in accordance with the national product label. The individual subject´s duration of participation was approximately 7-8 months. The period of observation for each subject was 6 months; another 10 to 15 days were anticipated for the study completion visit ("End-of-Treatment Visit"). The starting point of the observation was an infusion of ADVATE at baseline (dose: 50 ± 5 IU/kg) to determine incremental recovery (IR). For the ADVATE infusion to determine IR, a dose of 50 ± 5 IU/kg of ADVATE was given.

Figure 1: Study Design Schematic



Methods

Study participants

Inclusion criteria:

1. The subject or legally authorized representative (in case of study participants < 18 years of age) gave written informed consent to participate in the study
2. Subject of any age with hemophilia A
3. Subject was defined as previously treated patient (PTP):
    - Subject aged ≥ 6 years who has been previously treated with plasma-derived and/or recombinant FVIII concentrate(s) for a minimum of 150 exposure days (EDs)
    - Subject aged < 6 years who has been previously treated with plasma-derived and/or recombinant FVIII concentrate(s) for a minimum of 50 EDs
4. Subject with negative history of FVIII inhibitors and negative inhibitor at screening defined as less than 0.6 Bethesda units (BU)/mL (Nijmegen-modified Bethesda assay)
5. Subject was human immunodeficiency virus negative (HIV-); or HIV+ with stable disease and CD4+ count ≥ 200 cells/mm3, as confirmed by central laboratory at screening
6. Subject was hepatitis C virus negative (HCV-) by antibody or polymerase chain reaction (PCR) testing (if positive, antibody titer would be confirmed by PCR), as confirmed by central laboratory at screening; or HCV+ with chronic stable hepatitis
7. The subject was willing and able to comply with the requirements of the protocol

Exclusion criteria:

1. Subject who had known hypersensitivity to mouse or hamster proteins or to any of the excipients of FVIII concentrates
2. Subject diagnosed with bleeding disorder(s) other than congenital hemophilia A, such as acquired hemophilia A, von Willebrand´s disease (VWD) or thrombocytopenia (platelet count < 100,000/mL)
3. Subject who had received treatment for hemophilia A with non-FVIII products/concentrates (eg, emicizumab [Hemlibra®]) in the 6 months prior to screening
4. Subject who had severe chronic hepatic dysfunction [eg, ≥ 5 times upper limit of normal alanine aminotransferase (ALT), aspartate aminotransferase (AST) or INR > 1.5 as confirmed by central laboratory at screening]
5. Subject planned, or is likely to have, surgery during the study period
6. Subject who had a clinically significant medical, psychiatric, or cognitive illness, or recreational drug/alcohol use that, in the opinion of the investigator, would affect subject's safety or compliance
7. Subject currently receiving or was scheduled to receive during the course of the study, an immunomodulating drug (eg, corticosteroid agents at a dose equivalent to hydrocortisone greater than 10 mg/day, or α-interferon) other than antiretroviral chemotherapy
8. Subject having had participated in another clinical study involving an investigational product (IP) or investigational device within 30 days prior to enrollment or was scheduled to participate

in another clinical study involving an IP or investigational device during the course of this study.

9. Subject was a family member or employee of the investigator

Treatments

All subjects were on prophylaxis treatment, but whenever any subject had breakthrough bleeding, they were treated with additional doses of ADVATE (on-demand).

ADVATE, single-dose vials, administered by bolus injection over a period of ≤ 5 minutes.

Duration of Treatment: Approximately 7-8 months

• Duration of screening period: up to 45 days (until Day 0/Baseline Visit)

• Duration of treatment period: 6 months

• End-of-Treatment Visit: 10-15 days

Objective(s)

The primary objective of this study was to assess the safety of ADVATE based on serious adverse events (SAEs) (including FVIII inhibitors) that were possibly related to ADVATE. The secondary objectives were to assess the safety of ADVATE based on AEs and changes in laboratory parameters, to assess the efficacy of prophylactic treatment with ADVATE, and to assess the efficacy of on-demand treatment with ADVATE in the control of bleeding episodes.

Outcomes/endpoints

Primary Endpoint:

- Incidence of SAEs (including FVIII inhibitor formation) that were at least possibly related to ADVATE

Secondary Endpoints:

- Incidence of non-serious AEs that were at least possibly related to ADVATE
- Clinically significant changes in clinical laboratory parameters (hematology and clinical chemistry)
- Annualized bleeding rate (ABR) with prophylactic use of ADVATE
- Total number of infusions and the average number of infusions per week per month during prophylactic treatment
- Total and average body mass adjusted consumption of ADVATE per week per month during prophylactic treatment
- Overall hemostatic efficacy rating for treatment of bleeding episodes
- Number of ADVATE infusions required to achieve bleed resolution
- Body mass adjusted consumption of ADVATE per bleeding episode

Sample size

50 subjects were planned, enrolled, and analyzed for safety and efficacy.

Randomisation and blinding (masking)

Not applicable.

Statistical Methods

The statistical analysis for this study was descriptive in nature. Descriptive statistics included specifically, but not exclusively, arithmetic mean, standard deviation, medians, quartiles, interquartile range, minimum, maximum, proportions, frequency counts, and 95% confidence intervals of point estimates.

Results

Recruitment/Participant flow/Number analysed

Overall, 62 subjects were screened for the study. Of the 62 screened subjects, 12 subjects were considered screen failures. These subjects either did not meet the inclusion criteria (9 [75.0%] subjects), withdrew the consent (2 [16.7%] subjects), or were screened out of the window period (1 [8.3%] subject). Fifty subjects were found eligible for the study and were included both in the effectiveness full analysis set (EFAS) and the safety analysis set (SAS). Only 1 (2.0%) subject did not complete the study and the reason for termination from the study was that the subject withdrew the consent.

Baseline data

Demographics

All subjects were males and of Asian ethnicity. Overall mean ±standard deviation (SD) age, weight and height of subjects, and body mass index was 19.5±13.01 years, 48.5±20.95 kg, 152.0±22.68 cm, and 19.9±5.42 kg/m2, respectively.

Of the 50 subjects enrolled in the study, 4 subjects were <6 years of age, 10 subjects each were 6 to <12 years of age and 12 to <16 years of age, and 26 subjects were ≥16 years of age.

Assessor`s comment

According to the listing there were 6 additional adolescents being 16 and 17 years of age. Taken together the paediatric population comprises 30 subjects <18 years of age. In general, the whole study population is quite young which is displayed by the mean age of 19.5 years.

Hemophilia history

Summary statistics for deficient factor level and counts and percentage for disease severity were provided for those subjects diagnosed with hemophilia A prior to the enrollment. The mean ±SD deficient factor level was 1.8±5.52%. The disease severity was reported as mild in 1 (2.0%) subject, moderate in 2 (4.0%) subjects, and severe in 47 (94.0%) subjects. Subjects who received prophylactic treatment reported 3 bleeds (2 subjects) per month and 129 bleeds (21 subjects) per regimen period. Subjects who received on-demand treatment reported 180 bleeds (25 subjects) per month and 117 bleeds (22 subjects) per regimen period.

Assessor`s comment

In this study, patients with mild and moderate disease severity were also included. The two moderate cases had a factor VIII activity of 2% and <2%, respectively. Most subjects (n=47) suffered from severe haemophilia A with factor VIII activity <1%. However, a factor VIII activity of < 40% is listed for a subject with mild disease severity. Further information is required with regards to bleeding and treatment history of this subject (eligibility criteria) including data on performance during the study.

FVIII antigen

At screening, the mean ±SD for FVIII antigen was 1.5±2.83 IU/dL with a median of 0.8. All subjects showed low range indicator.

FVIII activity

At screening, the mean ±SD for FVIII activity was 1.9±8.65% with a median of 0.5. Forty-nine (98.0%) subjects showed low range indicator.

Medical history

Overall, 27 (54.0%) subjects reported at least 1 medical condition at the screening visit. The most frequently reported system organ classes (SOCs) in medical history were musculoskeletal and connective tissue disorders (26 [52.0%] subjects) and general disorders and administration site conditions (3 [6.0%] subjects).

Prior and concomitant medications

Of the 50 subjects, only 1 (2.0%) subject reported use of a prior medication (rabies vaccine inactivated [Vero]).

Five (10.0%) subjects reported use of at least 1 concomitant medication; 3 (6.0%) subjects were taking analgesic (paracetamol), and 1 (2.0%) subject each was taking calcium channel blockers (levamlodipine) and psychoanaleptics (imipramine hydrochloride). The concomitant use of non-drug therapies was not reported during the study.

Measurements of treatment compliance

The mean ±SD (%) was calculated to be 99.9±0.47, which was a very high compliance rate indicating that all subjects adhered to the treatment regimen as expected.

Efficacy results

Annualized Bleeding Rate

The point estimate (95% confidence interval [CI]) for the total ABR was 2.65 (1.807:3.886). The ABR was further categorized based on the location of bleed and type of bleed. The point estimate (95% CI) values by location of bleed were 2.33 (1.568:3.472), 0.04 (0.006:0.284), 0.16 (0.047:0.547), and 0.12 (0.024:0.588) for joint, soft tissue, muscle, and other location (mouth, gums, or nose), respectively. The point estimate (95% CI) values by type of bleed were 1.86 (1.231:2.818), 0.20 (0.052:0.782), and 0.59 (0.203:1.693) for spontaneous bleed, injury bleed, and unknown bleed, respectively (Table 1).

Table 1. Summary of Generalized Linear Model for Annualized Bleeding Rate with Prophylactic Use of ADVATE - EFAS (N=50)

Category	Statistics	Overall (N=50)
Total ABR		
	n	50
	Estimate	2.65
	Standard error	0.195
	95% CI for estimate	(1.807:3.886)
Location of bleed		
Joint		
	n	50
	Estimate	2.33
	Standard error	0.203
	95% CI for estimate	(1.568:3.472)
Soft tissue		
	n	50
	Estimate	0.04
	Standard error	1.000
	95% CI for estimate	(0.006:0.284)
Muscle		
	n	50
	Estimate	0.16
	Standard error	0.628
	95% CI for estimate	(0.047:0.547)
Other (mouth, gums or nose)		
	n	50
	Estimate	0.12
	Standard error	0.813
	95% CI for estimate	(0.024:0.588)
Type of bleed		
Spontaneous		
	n	50
	Estimate	1.86

Table 1. Summary of Generalized Linear Model for Annualized Bleeding Rate with Prophylactic Use of ADVATE - EFAS (N=50)

Category	Statistics	Overall (N=50)
	Standard error	0.211
	95% CI for estimate	(1.231:2.818)
Injury		
	n	50
	Estimate	0.20
	Standard error	0.692
	95% CI for estimate	(0.052:0.782)
Unknown		
	n	50
	Estimate	0.59
	Standard error	0.541
	95% CI for estimate	(0.203:1.693)

ABR=annualized bleeding rate; CI=confidence interval; EFAS=effectiveness full analysis set; n=subject count
Annualized bleeding rate during the prophylactic treatment was assumed to have a negative binomial distribution, and the mean ABR (95% CI) was estimated using a generalized linear model with logarithmic link function by keeping number of bleeds as dependent variable and the log time of the observed prophylactic treatment period as offset variable.
Source: TAK-761-4009 Final Clinical Study Report, Table 7

Overall, there were no bleeds observed in 22 subjects throughout the study period. The mean ±SD bleeding rate for the total ABR was 2.62±3.82 (median: 2.0). The ABR was further categorized based on the location of bleed and type of bleed. The mean ±SD bleeding rate per subject by location of bleed were 2.31±3.47, 0.04±0.28, 0.16±0.68, and 0.12±0.62 for joint, soft tissue, muscle, and other location (mouth, gums, or nose), respectively; it was not estimable for body cavity and intracranial. The mean ±SD bleeding rate per subject by type of bleed were 1.84±2.80, 0.20±0.94, and 0.58±2.35 for spontaneous bleed, injury bleed, and unknown bleed, respectively.

Assessor`s comment

The ABR for prophylactic treatment with ADVATE is in the usual range of standard half-life factor VIII products. The further categorization of ABR is not regarded meaningful due to the low number of bleeds and the unequal distribution of different types and locations.

The presentation of ABR obtained in study TAK-761-4009 covers the entire study population. To enable an assessment of ABR in the paediatric subset, the MAH should provide a separate analysis of ABR collected in study participant <18 years of age (i.e. <6 years, 6 to 12 years, 12-18 years).

Number of Infusions

The summary of total number of infusions and the average number of infusions per week and per month during prophylactic treatment is presented in Table 2. Overall, the mean ±SD number of

infusions was 65.8±22.92, with an average (mean ±SD) of 2.5±0.87 infusions per week and 11.0±3.76 infusions per month during prophylactic treatment.

Table 2. Summary of Total Number of Infusions and the Average Number of Infusions Per Week and Per Month During Prophylactic Treatment - EFAS (N=50)

Category	Statistics	Overall (N=50)
Total number of infusions		
	n	50
	Mean	65.8
	SD	22.92
	Median	72.5
	Range (Min:Max)	(26.0:94.0)
	IQR (Q1:Q3)	(49.0:88.0)
Average number of infusions (per week)		
	n	50
	Mean	2.5
	SD	0.87
	Median	2.8
	Range (Min:Max)	(1.0:3.5)
	IQR (Q1:Q3)	(2.0:3.4)
Average number of infusions (per month)		
	n	50
	Mean	11.0
	SD	3.76
	Median	12.1
	Range (Min:Max)	(4.3:15.1)
	IQR (Q1:Q3)	(8.6:14.6)

CI=confidence interval; EFAS=effectiveness full analysis set; IQR=interquartile range; Max=maximum; Min=minimum; n=subject count; Q=quartile; SD=standard deviation
Source: TAK-761-4009 Final Clinical Study Report, Table 9

Assessor`s comment

In general, the mean value of 2.5 infusions per week matches with the usual dosing schedule. But, due to the observed range there is at least one case with only 1 infusion per week, which is not regarded sufficient for standard half-life FVIII product. The applicant should comment.

Body Mass Adjusted Consumption of Advate

The summary of total and average body mass adjusted consumption of Advate per week and per month during prophylactic treatment is presented in Table 3. Overall, the mean ±SD total body mass adjusted consumption was 1739.7±621.18 IU/kg, with an average (mean ±SD) body mass adjusted consumption of 67.1±24.12 IU/kg per week and 291.7±104.80 IU/kg per month.

Table 3. Summary of Total and Average Body Mass Adjusted Consumption of Advate Per Week and Per Month During Prophylactic Treatment - EFAS (N=50)

Category	Statistics	Overall (N=50)
Total body mass adjusted consumption		
	n	50
	Mean	1739.7
	SD	621.18
	Median	1854.1
	Range (Min:Max)	(548.0:3259.6)
	IQR (Q1:Q3)	(1199.2:2141.2)
Average body mass adjusted consumption (per week)		
	n	50
	Mean	67.1
	SD	24.12
	Median	71.9
	Range (Min:Max)	(20.8:120.7)
	IQR (Q1:Q3)	(45.6:84.1)
Average body mass adjusted consumption (per month)		
	n	50
	Mean	291.7
	SD	104.80
	Median	312.6
	Range (Min:Max)	(90.6:524.6)
	IQR (Q1:Q3)	(198.0:365.2)

CI=confidence interval; EFAS=effectiveness full analysis set; IQR=interquartile range; Max=maximum; Min=minimum; n=subject count; Q=quartile; SD=standard deviation
Note: Body mass adjusted consumption (IU/kg) was derived as the total units infused (IU) divided by the last available body weight (kg) prior to the infusion.
Source: TAK-761-4009 Final Clinical Study Report, Table 10

Hemostatic Efficacy Rating for Treatment of Bleeding Episodes

Of the 51 hemostatic efficacy rating responses obtained after on-demand treatment (ie, breakthrough bleeds during prophylaxis treatment), 21 (41.2%), 26 (51.0%), and 4 (7.8%), were rated as excellent, good, and moderate, respectively Table 4.

Table 4. Summary of Overall Hemostatic Efficacy Rating for Treatment of Bleeding Episodes – EFAS (N=50)

Category	Statistics	Overall (N=50)
Number of infusions (on-demand)		
	Total hemostatic efficacy rating response, n	51
	Excellent	21 (41.2%)
	Good	26 (51.0%)
	Moderate	4 (7.8%)
	None	0 (0.0%)

EFAS=effectiveness full analysis set; n=subject count
Notes: Percentages were calculated using total hemostatic efficacy rating response count as denominator.
On-demand means breakthrough bleeding.
Source: TAK-761-4009 Final Clinical Study Report, Table 11

A total of 51 hemostatic efficacy rating responses were reported for treatment of bleeding episodes, of which 21 (41.2%), 26 (51.0%), 4 (7.8%), were rated as excellent, good, and moderate, respectively.

A total of 3245 effectiveness rating response were reported for prophylactic treatment, of which 1927 (59.4%), 1267 (39.0%), 51 (1.6%), were rated as excellent, good, and moderate, respectively.

Of the 51, total On-Demand treated bleeds (ie, breakthrough bleeds during prophylaxis treatment), classified by Location of bleed; at Joint were rated as excellent for 21 (41.2%), good for 22 (43.1%), and moderate for 4 (7.8%), respectively; at Soft Tissue was good for 1 (2.0%); and at Other (Mouth, Gums or Nose) was good for 3 (5.9%).

Of the 51, total On-Demand treated bleeds, classified by Type of bleed; into Spontaneous were rated as excellent for 18 (35.3%), good for 14 (27.5%), and moderate for 3 (5.9%), respectively; into Injury were rated as excellent for 2 (3.9%), and good for 2 (3.9%); into Unknown were rated as excellent for 1 (2.0%), good for 10 (19.6%), and moderate for 1 (2.0%), respectively.

Of the 51, total On-Demand treated bleeds, classified by Severity of bleed; into Minor were rated as excellent for 19 (37.3%), good for 12 (23.5%), and moderate for 1 (2.0%), respectively; into Moderate were rated as excellent for 2 (3.9%), good for 14 (27.5%), and moderate for 3 (5.9%), respectively. There were no major; or life or limb threatening bleeds.

Assessor`s comment

An effectiveness assessment of prophylactic treatment has been described in the CSR. The MAH should comment on this procedure with regards to the applied scale and its informative value.

Number of Advate Infusions Required to Achieve Bleed Resolution

A total of 28 subjects had 67 bleeds during the study; 24 subjects required either 1, 2, or 3 Advate infusions (mean ±SD: 1.2±0.43) to achieve resolution for 51 bleeds (Table 5).

Table 5. Summary of Number of Advate Infusions Required to Achieve Bleed Resolution – EFAS (N=50)

Category	Statistics	Overall (N=50)
Number of infusions (on-demand)		
	Subjects who experienced bleeds	24
	Total bleeds, n	51
	Mean	1.2
	SD	0.43
	Median	1.0
	Range (Min:Max)	(1.0:3.0)
	IQR (Q1:Q3)	(1.0:1.0)

EFAS=effectiveness full analysis set; IQR=interquartile range; Max=maximum; Min=minimum; n=subject count; Q=quartile; SD=standard deviation
Notes: Total 28 subjects had 67 bleeds; however, among them, 24 subjects required Advate infusion for the management of 51 bleeds.
On-demand means breakthrough bleeding.
Source: TAK-761-4009 Final Clinical Study Report, Table 16

Among them, 23 subjects required 1.2±0.45 infusions to achieve resolution for 47 joint bleeds, 1 subject required 1.0±0.0 infusion to achieve resolution for 1 soft tissue bleed, and 2 subjects required 1.0±0.0 infusion to achieve resolution for 3 other bleeds (mouth, gums, or nose).

Nineteen subjects required 1.3±0.51 infusions to achieve resolution for 35 spontaneous bleeds, 2 subjects required 1.0±0.0 infusion to achieve resolution for 4 injury bleeds, and 5 subjects required 1.1±0.0 infusion to achieve resolution for 12 unknown bleeds.

A total of 21 subjects required 1.1±0.34 infusions to achieve resolution for 32 minor bleeds and 7 subjects required 1.3±0.56 infusions to achieve resolution for 19 moderate bleeds. None of the subjects reported major, life- or limb-threatening bleeds.

Assessor`s comment

No ADVATE infusion has been required in 16 bleeds. The MAH should clarify whether other concomitant treatments have been administered in these cases.

Body Mass Adjusted Consumption of Advate per Bleeding Episode

The mean ±SD body mass adjusted consumption of Advate was 33.6±19.29 IU/kg for the 24 subjects who reported 51 bleeds. The mean ±SD body mass adjusted consumption of Advate was 33.9±19.77 IU/kg for the 23 subjects who reported 47 joint bleeds, 50.0±0.0 IU/kg for the subject who reported

1 soft tissue bleed, and 22.8±1.72 IU/kg for the 2 subjects who reported 3 other (mouth, gums or nose) bleeds.

The mean ±SD body mass adjusted consumption of Advate was 37.5±21.70 IU/kg for the 19 subjects who reported 35 spontaneous bleeds, 34.0±10.70 IU/kg for the 2 subjects who reported 4 injury bleeds, and 22.0±3.24 IU/kg for the 5 subjects who reported 12 unknown bleeds.

The mean ±SD body mass adjusted consumption of Advate was 33.2±15.14 IU/kg for 21 subjects who reported 32 minor bleeds and 34.2±25.27 IU/kg for 7 subjects who reported 19 moderate bleeds. Major, life- or limb-threatening bleeds were not reported.

Incremental Recovery

The mean ± SD pre-dose values were 1.3 ± 1.24, 1.3 ± 0.97, 3.1 ± 6.36 % IU/dl at Baseline Visit, Visit 2, and End of Treatment Visit, respectively. The Mean ± SD post-dose values were 86.0 ± 37.57, 99.3 ± 36.15, 94.7 ± 54.72 % IU/dl at Baseline Visit, Visit 2, and End of Treatment Visit, respectively. There was an increase in the mean values of the incremental recovery over the study period.

Safety results

Extent of Exposure

The mean ±SD treatment exposure was 6.0±0.44 months and the duration of treatment ranged from 3.1 to 6.7 months.

Adverse Events

Overall, 9 AEs were reported in 6 (12.0%) subjects. Of these, 6 AEs were reported in 5 paediatric subjects (<18 years of age). All AEs were mild in intensity, not related to the study drug, and resolved completely. The dose of the drug was not changed due to any of the AEs reported. No deaths or SAEs (including FVIII inhibitor formation) were reported in this study. None of the subjects discontinued the study or was withdrawn from the treatment due to AEs. Three (6.0%) subjects received concomitant medication/therapies for the treatment of 4 AEs.

Of the 9 AEs reported in 6 (12.0%) subjects,

- Six events were reported in 4 (8.0%) subjects within the SOC injury, poisoning and procedural complications (preferred terms [PTs]: animal bite [1], joint injury [3], and skin laceration [2])
- Two events were reported in 2 (4.0%) subjects within the SOC general disorders and administration site conditions (PT: pyrexia [2])
- One event was reported in 1 (2.0%) subject within the SOC infections and infestations (PT: varicella [1]).

Clinical Laboratory Evaluations

None of the subjects reported clinically significant changes for any of the hematology and clinical chemistry parameters assessed.

Incidence of FVIII inhibitor development

The incidence of FVIII inhibitor development was summarized by high-titer (> 5 BU) and low-titer (0.6-5 BU). The point estimate for the incidence of FVIII inhibitor development was calculated to be 0.35, 0.38, 0.4, 0.38, and 0.37 BU/mL at visits (Screening, Baseline, Visit 1, Visit 2, and End of Treatment) respectively. No subjects developed confirmed FVIII inhibitors, since the FVIII inhibitor value was not ≥ 0.6 Bethesda units (BU/mL).

Assessor`s comment

Overall, the number of AEs observed in study TAK-761-4009 with ADVATE was low. In addition, all AEs were mild in intensity. No treatment-related AEs and no SAE have been reported. There were no further safety concerns.

According to the listing 6 AEs were reported in 5 paediatric subjects (<18 years of age). The other 3 AEs (all joint injury) occurred in a.

With regard to the AEs animal bite, skin laceration and varicella, causality assessment in paediatric subjects is agreed. But, there were also 2 events of pyrexia which are common ADRs of ADVATE treatment.

Nevertheless, the rate of AEs was surprisingly low during this study and the incidence of related AEs was zero. Questions pertaining to reporting and causality assessment of AEs arise. The MAH is asked to comment.

2.3.3. Discussion on clinical aspects

As part of this Article 46 procedure, the MAH submitted the final report of study TAK-761-4009 together with an Addendum to the Clinical Overview. Study TAK-761-4009 was a Phase 4, multicenter, open label, prospective, interventional, single-group, post-marketing study in previously treated hemophilia A patients (PTPs) in India receiving ADVATE under standard clinical practice. The purpose of this study was to evaluate the safety and efficacy of ADVATE when used under standard clinical practice in previously treated hemophilia A patients (PTPs) in India.

The primary objective of this study was to assess the safety of ADVATE based on serious adverse events (SAEs) (including FVIII inhibitors) that were possibly related to ADVATE. The secondary objective was to assess the safety of ADVATE based on adverse events (AEs) and changes in laboratory parameters. Efficacy assessment of prophylactic treatment and of on-demand treatment with ADVATE in the control of bleeding episodes were also secondary objectives.

The study was conducted at four centers across India. Key assessments included incidence of possibly or probably related SAEs related to ADVATE, response to treatment, annualized bleed rate (ABR), FVIII inhibitor development, number of infusions required for bleed resolution, total and average body mass adjusted consumption of ADVATE during treatment and the overall haemostatic efficacy.

Overall, 62 subjects were screened, while 50 subjects were found eligible for the study. Of the 50 subjects enrolled 30 subjects were <18 years of age showing a generally young study population with a mean age of 19.5 years. According to disease history, the study population included subjects with mild (n=1), moderate (n=2) and severe (n=47) Hemophilia A. The two moderate cases had a factor VIII activity of 2% and <2%, respectively. Most subjects (n=47) suffered from severe haemophilia A with factor VIII activity <1%. However, a factor VIII activity of < 40% is listed for a subject with moderate disease severity. Meeting of eligibility criteria and performance during the study need to be

clarified for this case. All enrolled subjects were on prophylaxis treatment, but whenever any subject had break-through bleeding, they were treated with additional doses of ADVATE (On-Demand).

Altogether, 9 adverse events were reported in 6 (12.0%) subjects. All the AEs were mild in intensity, not related to the study drug, resolved completely, and required no change in the dose of the drug for its management. No death or SAEs were reported in this study. None of the subjects developed FVIII inhibitor antibody. None of the subjects discontinued the study or was withdrawn from the treatment because of the AEs. Since the rate of AEs and the incidence of related AEs were surprisingly low during this study, questions pertaining to reporting and judgement of AEs arise.

ABR during prophylactic treatment was estimated using the Generalized Linear Model (GLM) and the point estimate (95% CI) for the total ABR was 2.65 (1.807:3.886). Similar findings were obtained when the total ABR was summarized descriptively and the total ABR, bleeding rate per subject was calculated as (mean ± SD) 2.62 ± 3.82 with a median 2.0. The ABR for prophylactic treatment with ADVATE is in the usual range of standard half-life factor VIII products. The further categorization of ABR is not regarded meaningful due to the low number of bleeds and the unequal distribution of different types and locations. However, the presentation of ABR obtained in study TAK-761-4009 covers the entire study population. To enable an assessment of ABR in the paediatric subset, the MAH should provide a separate analysis of ABR collected in study participant <18 years of age (i.e. <6 years, 6 to 12 years, 12-18 years).

On average the number of infusions (per week) was (mean ± SD) 2.5 ± 0.87 and the average body mass adjusted consumption (per week) was (mean ± SD) 67.1 ± 24.12 IU/kg. In general, the mean value of 2.5 infusions per week matches with the usual dosing schedule. But, the data display cases with significantly less infusions per week, which is not regarded sufficient for a FVIII product with standard half-life. The average body mass adjusted consumption data also appear to be quite low.

Hemostatic efficacy rating response for the bleeds that occurred during On-Demand treatment was rated as excellent in 41.2% and good in 51.0%. Overall, 22 subjects had zero bleeds throughout the study period. A total of 28 subjects had 67 bleeds. Only 24 subjects required either 1, 2 or 3 infusions of ADVATE to achieve complete bleed resolution of 51 bleeds. Most bleedings were spontaneous (n=35) and occurred in joints (n=47). There were 32 minor and 19 moderate bleeds. None of the subjects reported major, life or limb threatening bleeds. The Body mass adjusted consumption of ADVATE for 51 bleeds in 24 subjects were 33.6 ± 19.29 IU/kg. There was an increase in the mean values of the incremental recovery over the study period.

In conclusion, the provided data showed a favourable safety profile of ADVATE in the investigated study population. There were no new safety concerns observed in this study. ABR during prophylactic treatment was comparable to other FVIII products with a standard half-life. The data apply for haemophilia A patients in India.

3. Rapporteur's overall conclusion and recommendation

In summary, the post-marketing data collected in study TAK-761-4009 do not change the favourable benefit risk profile of ADVATE in the approved indications. The presented data do not warrant any update of the Product Information and no regulatory actions are expected to be required. However, prior to a final recommendation, the MAH should provide some additional information as outlined in detail in section 4 below.

☒ **Not fulfilled: refer to section 4**

4. Request for supplementary information

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

1. In this study, patients with mild and moderate disease severity were also included. The two moderate cases had a factor VIII activity of 2% and <2%, respectively. Most subjects (n=47) suffered from severe haemophilia A with factor VIII activity <1%. However, a factor VIII activity of < 40% is listed for a subject with mild disease severity. Further information is required with regard to bleeding and treatment history of this subject (eligibility criteria) including data on performance during this study.
2. The presentation of ABR obtained in study TAK-761-4009 covers the entire study population. To enable an assessment of ABR in the paediatric subset, the MAH should provide a separate analysis of ABR collected in study participant <18 years of age (i.e. <6 years, 6 to 12 years, 12-18 years).
3. An effectiveness assessment of prophylactic treatment has been described in the CSR. The MAH should comment on this procedure with regard to the applied scale and its informative value.
4. A mean value of 2.5 infusions of ADVATE per week matches with the usual dosing schedule. But, the data display cases with significantly less infusions per week, which is not regarded sufficient for a FVIII product with standard half-life. The average body mass adjusted consumption data also appear to be quite low. The MAH should comment.
5. No ADVATE infusion has been required in 16 bleeds. The MAH should clarify whether other concomitant treatments have been used in these cases.
6. According to the listing 6 AEs were reported in 5 paediatric subjects (<18 years of age). With regard to the AEs animal bite, skin laceration and varicella, causality assessment in paediatric subjects is agreed. But, there were also 2 events of pyrexia which are common ADRs of treatment with ADVATE. Overall, the rate of AEs was surprisingly low during this study and the incidence of related AEs was zero. Questions pertaining to reporting and causality assessment of AEs arise. The MAH is asked to comment.

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

5. MAH responses to Request for supplementary information

Question 1

In this study, patients with mild and moderate disease severity were also included. The two moderate cases had a factor VIII activity of 2% and <2%, respectively. Most subjects (n=47) suffered from severe haemophilia A with factor VIII activity <1%. However, a factor VIII activity of < 40% is listed for a subject with mild disease severity. Further information is required with regard to bleeding and treatment history of this subject (eligibility criteria) including data on performance during this study.

Summary of the Applicant's Response

The above-referred Subject was aged and had a documented case of hemophilia A since 2007. The subject had 150 exposure days (EDs) with recombinant factor VIII (FVIII) concentrate(s) as confirmed by the source data and the same is also reflected in the electronic data capture.

The relevant inclusion criteria from Section 5.1 of the protocol are listed below.

2. Subject of any age with hemophilia A

3. Subject is defined as a previously treated patient:

- ***Subject aged ⩾6 years that has been previously treated with plasma-derived and/or recombinant FVIII concentrate(s) for a minimum of 150 EDs.***
- ***Subject aged <6 years that has been previously treated with plasma-derived and/or recombinant FVIII concentrate(s) for a minimum of 50 EDs.***

Hemophilia severity <1% was not an inclusion criterion. Based on the medical and treatment history, the subject met all the inclusion criteria specified in the protocol, and hence, after confirming their eligibility, the subject was enrolled in the study.

Concerning the overall performance, only 1 bleeding episode was recorded for the subject during the study, and as the bleeding was spontaneous and minor in severity (left arm, muscular bleed), no ADVATE treatment was given, as per investigator discretion.

No adverse events (AEs) were recorded for the subject during the treatment period.

The overall effectiveness of the drug throughout the study was Excellent (74.5%) and Good (25.5%), as per investigator and subject assessment.

Assessment of the Applicant's Response

The applicant provided the requested information. Eligibility criteria were met by the subject with moderate haemophilia A. No ADVATE treatment has been required during the study period.

Conclusion

Point resolved.

Question 2

The presentation of ABR obtained in study TAK-761-4009 covers the entire study population. To enable an assessment of ABR in the paediatric subset, the MAH should provide a separate analysis of ABR collected in study participant <18 years of age (i.e. <6 years, 6 to 12 years, 12-18 years).

Summary of the Applicant's Response

As suggested, a subgroup analysis was performed to enable an assessment of annualized bleeding rate (ABR) in pediatric subjects. Kindly refer to Table 2.a and Table 2.b.

The summary of Generalized Linear Model for ABR with prophylactic use of ADVATE by Pediatric Age Group - Effectiveness full analysis set (N=32) is presented in Table 2.a. The overall point estimate (95% confidence interval [CI]), for the total ABR in the study participants ≤18 years was 2.51 (1.393:4.534). For the age groups ≤6 years, >6 to ≤12 years, and >12 to ≤18 years, the point estimate (95% CI) for the total ABR was 0.36 (0.050:2.540), 3.95 (1.416:11.040), and 2.50 (1.187:5.253), respectively.

Table 2.a Summary of Generalized Linear Model for Annualized Bleeding Rate with prophylactic use of ADVATE by Pediatric Age Group - Effectiveness Full Analysis Set (N=32)

ABR [a]	Parameter	Age ≤6 Years (N=6)	Age >6 to ≤12 Years (N=9)	Age >12 to ≤18 Years (N=17)	Overall (N=32)
Total	n	6	9	17	32
	Estimate	0.36	3.95	2.50	2.51
	Standard Error	1.000	0.524	0.379	0.301
	95% CI for Estimate	(0.050:2.540)	(1.416:11.040)	(1.187:5.253)	(1.393:4.534)

ABR: annualized bleeding rate; CI: confidence interval; GLM: generalized linear model; N: all subjects in the effectiveness full analysis set; n: number of subjects in pediatric age group.
[a] Annualized bleeding rates during the prophylactic treatment were assumed to have a negative binomial distribution, and the mean ABRs (95% CI) were estimated using a GLM with logarithmic link function by keeping number of bleeds as dependent variable and the log time of the observed prophylactic treatment period as offset variable.
Source: Data on file.

The summary of ABR by Pediatric Age Group - Effectiveness full analysis set (N=32) is presented in Table 2.b. The overall mean±standard deviation (SD) bleeding rate per subject for the total ABR in study participants ≤18 years was calculated as 2.48±4.43 (median 0.0). The mean±SD bleeding rate per subject for the total ABR was calculated as 0.32±0.79 (median 0.0), 3.94±5.80 (median 2.0), and 2.47±4.25 (median 1.9) for the age groups ≤6 years, >6 to ≤12 years, and >12 to ≤18 years, respectively.

Table 2.b Summary of Annualized Bleeding Rate by Pediatric Age Group - Effectiveness Full Analysis Set (N=32)

Category	Variable	Statistics	Age ≤6 Years (N=6)	Age >6 to ≤12 Years (N=9)	Age >12 to ≤18 Years (N=17)	Overall (N=32)
Total ABR	Number of Subjects	n	6	9	17	32
	Bleeding Rate per Subject	Mean	0.32	3.94	2.47	2.48
		95% CI for the Mean	(0.00:1.15)	(0.00:8.40)	(0.29:4.66)	(0.89:4.08)
		SD	0.79	5.80	4.25	4.43
		Median	0.0	2.0	1.9	0.0
		Range (Min:Max)	(0.0:1.9)	(0.0:15.5)	(0.0:15.4)	(0.0:15.5)
		IQR (Q1:Q3)	(0.0:0.0)	(0.0:4.0)	(0.0:2.0)	(0.0:2.0)

ABR: annualized bleeding rate; CI: confidence interval; IQR: interquartile range; max: maximum; min: minimum; Q1: quartile 1; Q3: quartile 3; SD: standard deviation.
Overall, 22 subjects had zero bleeds throughout the study period.
Annualized Bleeding Rate was defined as (number of bleeding episodes during the study period / total number of study period days) × 365.25.
Source: Data on file.

Assessment of the Applicant's Response

A mean bleeding rate of 3.96 was observed in the age group between >6 and ≤12 years of age. This is a higher value than in the other groups. But, the subject number per subgroup was low and an ABR of about 4 is still in the expected range. Of note, the median value was 2.0 in this age group.

Conclusion

Point resolved.

Question 3

An effectiveness assessment of prophylactic treatment has been described in the CSR. The MAH should comment on this procedure with regard to the applied scale and its informative value.

Summary of the Applicant's Response

The procedure, regarding the applied scale and its informative value for the effective assessment of the prophylactic treatment is detailed below.

Assessment:

Total number (%) of treated bleeds and their corresponding hemostatic effectiveness ratings were assessed using an "**excellent-to-none**" **4-point Likert scale** by the subjects/caregiver (**subjects <12 years: caregiver, subjects ≥12 years: self-assessment**) for treatments given at home, or by the **investigator** for treatments given in the hospital/clinic.

Timepoints:

The overall effectiveness for prophylactic treatment was assessed at Visit 1 (1 month±1 week), Visit 2 (3 months±1 week), and during the End of Treatment Visit (6 months±1 week). Apart from these visits, the subject, or their caregiver graded the responses for treatments given at home in the subject's diary.

Notes:

It should be noted that, on average, a subject was administered with 2-3 infusions per week and after each administration, the subject/caregiver or the Investigator graded the response.

Subject diary responses included the responses subjects graded throughout the study period ie, at every infusion for a period of 6 months.

For one subject (), bleeding episode, ADVATE was administered, during an unscheduled visit.

Statistical Calculations and Results:

Overall effectiveness assessment for prophylactic treatment effectiveness was summarized by frequency and percentages.

Results can be found in TAK-761-4009 clinical study report, Listing 16.2.6.2.

Important Findings from the Listing:

None of the subjects graded the overall effectiveness assessment for prophylactic treatment response as "**none**".

The efficacy responses given during prophylactic treatment are detailed in Table 3.a.

A total of 3245 responses were recorded either by the caregiver/self in subject dairy and by the Investigator during the site visit. The responses were graded as excellent, good, or moderate.

Table 3.a Prophylactic Responses

	Excellent	Good	Moderate	None	Total
Total Prophylactic Responses	1927 (59.4%)	1267 (39.0%)	51 (1.6 %)	0 (0.0%)	3245
Visit 1 (1 Month)	26 (57.8%)	19 (42.2%)	0 (0.0%)	0 (0.0%)	45
Visit 2 (3 Month)	25 (56.8%)	19 (43.2%)	0 (0.0%)	0 (0.0%)	44
EOT (6 Month)	29 (65.9%)	15 (34.1%)	0 (0.0%)	0 (0.0%)	44
Subject Dairy (Throughout the study period ie, at every infusion for 6 months)	1847 (59.4%)	1214 (39.0%)	51 (1.6%)	0 (0.0%)	3112

EOT: end of treatment
Percentages were calculated using 'Total effectiveness rating response' count as denominator.
Source: Data on file.

For the 51 breakthrough bleeding episodes, ADVATE was administered on-demand by the caregiver/self and the response was graded (Table 3.b).

Table 3.b On-demand Responses

	Excellent	Good	Moderate	None	Total
Total On-demand Responses	21 (41.2%)	26 (51.0%)	4 (7.8%)	0 (0.0%)	51
Unscheduled Visit	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1
Subject Dairy (Throughout the study period ie, at every infusion for 6 months)	20 (40.0%)	26 (52.0%)	4 (8.0%)	0 (0.0%)	50

Percentages were calculated using 'Total effectiveness rating response' count as denominator.
Source: Data on file.

Assessment of the Applicant's Response

An "excellent-to-none" 4-point Likert scale has been used, which is quite rough but appears to be useful in this setting. Most of the treatment responses were rated by caregiver/self in subject dairy. With regard to the prophylactic responses subject assessment generally complies with assessment at visit. But, there were a small number of moderate ratings (1.6%). In addition, there were also four ratings of moderate response for on-demand treatment. But, no further conclusions are possible due to the low number of cases requiring on-demand treatment.

Overall, it can be concluded that prophylactic treatment with ADVATE was effective in the paediatric population.

Conclusion

Point resolved.

Question 4

A mean value of 2.5 infusions of ADVATE per week matches with the usual dosing schedule. But, the data display cases with significantly less infusions per week, which is not regarded sufficient for a FVIII product with standard half-life. The average body mass adjusted consumption data also appear to be quite low. The MAH should comment.

Summary of the Applicant's Response

Investigational product (IP) was administered at 2-3-day intervals. The majority of adult and pediatric subjects had 3-day infusion intervals. For subjects below 6 years, sites followed the prescription pattern based on the medical judgment of the investigator.

This is consistent with the current prescriber information:

Prophylaxis: "For long-term prophylaxis against bleeding in patients with severe hemophilia A, the usual doses are 20 to 40 IU of factor VIII per kg body weight at intervals of 2 to 3 days."

Pediatric population: "For on demand treatment dosing in paediatric patients (0 to 18 years of age) does not differ from adult patients.

In patients under the age of 6, doses of 20 to 50 IU of factor VIII per kg body weight 3 to 4 times weekly are recommended for prophylactic therapy."

A total of 24 subjects (site/subject numbers;) received 2 infusions per week at 3-day interval, and 3 subjects () under 6 years of age received 2 infusions per week at 3-day intervals, as per prescriber's information for prophylactic treatment. The remaining subjects who participated in the study received the 3 infusions per week at 2-day intervals, as per the prescriber's information.

The frequency of IP dose administration was based on the medical judgment of investigator. The average body mass-adjusted consumption data sheet for all 24 subjects with reference to the query is provided in Table 4.a.

Table 4.a Average Body Mass-adjusted Consumption Datasheet

Site #/Subject #	Age	IP Dose IU/kg (Baseline)	IP Dose IU/kg (Visit 1)	IP Dose IU/kg (Visit 2)	IP Dose IU/kg (EOT)
		50	21	21	55
		48	32	31	55
		23.58	23.26	50	44
		20	23	50	50
		50	22	22.62	50.79
		50	21.65	21.5	50
		50	20	13.32	50
		50	24	24	50
		50	23	25.41	50
		50	20	49	51.7
		50	50	40	50
		50.35	35.21	33.11	Subject withdrawn
		50.45	17.9	30.33	50
		48	50.9	31	50.1
		48.62	20.61	20.8	52
		50.18	34.12	32.6	50
		50.26	26.92	24.67	50
		50.38	46	50	40

CSR: clinical study report; EOT: end of treatment; IP: investigational product
Source: TAK-761-4009 CSR, Listing 16.2.1.1 and Listing 16.2.5.4.

Table 4.a Average Body Mass-adjusted Consumption Datasheet

Site #/Subject # Age	IP Dose IU/kg (Baseline)	IP Dose IU/kg (Visit 1)	IP Dose IU/kg (Visit 2)	IP Dose IU/kg (EOT)
	48	24	24	45
	52	21	21	54
	50	31	20	57
	50	22	20	55
	53	26	25	48
	55	37	18	54

Assessment of the Applicant's Response

Apart from baseline and end of study the applied dose was in the lower range for most of the subjects. The frequency of dosing followed the recommendations.

Conclusion

Point resolved.

Question 5

No ADVATE infusion has been required in 16 bleeds. The MAH should clarify whether other concomitant treatments have been used in these cases.

Summary of the Applicant's Response

Of all 16 bleeds referred to in the above query, 14 bleeding episodes were mild in severity and 2 bleeding episodes were moderate. There were no concomitant medications prescribed to the subjects for the bleeding episodes based on the medical judgment of investigator.

Table 5.a Bleeds That Did Not Require ADVATE Treatment

Site#/ Subject #	Age in Years	Bleeding Episode Cause	Location	Severity	ADVATE Treatment Given	Concomitant Medication
		Injury	Thumb Right Finger, (Joint)	Minor	No	No
		Unknown	Right shoulder (Joint)			
			Left Foot (Muscular)			
		Spontaneous	Right Knee (Joint)	Minor	No	No
			Left Elbow (Joint)			
			Left Ankle (Joint)			
			Left Elbow (Joint)			
			Left knee (Joint)			
		Spontaneous	Right Knee (Joint)	Minor	No	No
		Spontaneous	Right Knee (Joint)	Minor	No	No
			Right Leg (Muscular)			
		Spontaneous	Right Jaw (Joint)	Minor	No	No
			Right Jaw (Joint)	Moderate		
		Unknown	Left Arm (Muscular)	Minor	No	No
		Spontaneous	Right Elbow (Joint)	Moderate	No	No
		Spontaneous	Right Ankle (Joint)	Minor	No	No

CSR: clinical study report
Source: TAK-761-4009 CSR, Listing 16.2.6.1 and data on file.

Assessment of the Applicant's Response

No concomitant medications have been provided in these bleeds. Most of them were minor.

Conclusion

Point resolved.

Question 6

According to the listing 6 AEs were reported in 5 paediatric subjects (<18 years of age). With regard to the AEs animal bite, skin laceration and varicella, causality assessment in paediatric subjects is agreed. But, there were also 2 events of pyrexia which are common ADRs of treatment with ADVATE. Overall, the rate of AEs was surprisingly low during this study and the incidence of related AEs was zero. Questions pertaining to reporting and causality assessment of AEs arise. The MAH is asked to comment.

Summary of the Applicant's Response

With respect to the above query, 2 events of pyrexia were noted in the study, however, based on the investigator's judgment, the AEs were considered not related to the IP. The onset of both events was more than 12 hours from the last dose of IP and resolved within a day, hence correlation of AE with the IP could not be established.

Table 6.a Information on Events of Pyrexia

Site #/ Subject #	AE Term	Onset Date	Stop Date	Severity	Concomitant Medication/ Therapy	Drug Event Relationship as per PI	Outcome	Concomitant Medication	Last IP Dose Date/ Time
				Mild	Yes	Not related	Resolved		
				Mild	Yes	Not related	Resolved		

AE: adverse event; CSR: clinical study report; IP: investigational product; PI: primary investigator; PRN: pro re nata.
Source: TAK-761-4009 CSR, Listing 16.2.7.1 and data on file.

A total of 217 bleeding events were reported in the study. Since bleeding episodes are a symptom of the disease, they were not considered as AEs. However, bleeding events were rated as mild, moderate, and severe (as assessed by the investigator) and reported under specific study endpoints (eg, ABR).

Given that the study used real-world data and post-marketing surveillance, the total number of reported AEs were captured using information that was available from the subject diary and assessed by the investigator.

Assessment of the Applicant's Response

The 2 events of pyrexia occurred more than 12 hours after IP administration. Thus, the investigator's judgment as not related is agreed. Overall, it is recognized that the reporting rate of AEs is influenced by the kind of the study. In this case the study used real-world data and post-marketing surveillance.

Conclusion

Point resolved.

6. Rapporteur's overall conclusion and recommendation on the MAHs responses to RSI

☒ Fulfilled:

No regulatory action required.

Annex. Line listing of all the studies included in the development program

Not applicable. As declared by the MAH, the submitted study is not part of a clinical development program.