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Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Advate/Adynovi

International non-proprietary name: Octocog alfa/Rurioctocog alfa pegol

Procedure no.: EMA/H/C/000520/P46/101 & EMEA/H/C/004195/P46/011

Note

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

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Status of this report and steps taken for the assessment				
Current step	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Start of procedure	17 July 2023	17 July 2023	☐
☐	CHMP Lead Rapporteur Assessment Report	21 Aug 2023	21 Aug 2023	☐
☐	CHMP members comments	04 Sep 2023	04 Sep 2023	☐
☐	Updated CHMP Lead Rapporteur Assessment Report	07 Sep 2023	07 Sep 2023	☐
☐	CHMP adoption of conclusions:	14 Sep 2023	14 Sep 2023	☐
☐	Submission	20 Feb 2024	20 Feb 2024	☐
☐	Re-start	21 Feb 2024	21 Feb 2024	☐
☐	CHMP Rapporteur Assessment Report	06 Mar 2024	05 Mar 2024	☐
☐	CHMP members comments	11 Mar 2024	11 Mar 2024	☐
☐	Updated CHMP Rapporteur Assessment Report	14 Mar 2024	14 Mar 2024	☐
☒	CHMP adoption of conclusions:	21 Mar 2024	21 Mar 2024	☐

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1. Introduction

On 3rd July, the MAH submitted a completed paediatric study (060902) for ADVATE and ADYNOVI, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study AHEAD (060902) is a stand-alone study. The study is not part of the PIP or the clinical development program of ADVATE or ADYNOVI.

2.2. Information on the pharmaceutical formulation used in the study

Octocog alfa (ADVATE), is a third-generation recombinant factor VIII (FVIII) concentrate developed by Baxter Healthcare Corporation (now part of Takeda). ADVATE was first approved in the United States (US) in 2003. In Europe, ADVATE was registered on 02 Mar 2004 through a centralized procedure. As of 26 Aug 2022, ADVATE is approved in 77 countries worldwide. ADVATE is indicated for haemophilia A for the prevention and control of bleeding episodes.

Rurioctocog alfa pegol is a pegylated form of ADVATE with a 1.3 to 1.5 times extended half-life ($T_{1/2}$) due to addition of a 20 kDa polyethylene glycol (PEG). It was first licensed in the US in 2015 under the trade name ADYNOVATE, then granted marketing authorization for patients 12 years and older by the European Commission on 08 Jan 2018 under the trade name ADYNOVI. As of 12 Nov 2022, ADYNOVATE/ADYNOVI is approved in 32 countries worldwide. It is indicated for treatment and prophylaxis of bleeding in patients with haemophilia A.

In the EU, ADVATE is indicated in all age groups, while ADYNOVI is indicated for patients ≥12 years of age.

Both ADVATE and ADYNOVI are produced by recombinant DNA technology in the Chinese Hamster Ovary (CHO) cell line without the addition of any exogenous human- or animal-derived additives thereby eliminating the risk of potential contamination with viruses and/or prions. Both products are provided as powder and solvent for solution for intravenous injection.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report(s) for:

- Study 060902: ADVATE/ADYNOVI Haemophilia A Outcome Database (AHEAD)

An 11-year, single-arm, prospective, non-interventional study, sponsored by the MAH, with a goal to document and compare long-term outcomes of patients receiving ADVATE or ADYNOVI in routine clinical practice in terms of quality of life, haemophilia-related co-morbidity, drug utilization, effectiveness and safety.

Since the study used two medicinal products of the Company authorised in the centralised procedure, parallel applications with identical content in terms of Module 2 and 5 were submitted to the Agency for both ADVATE (eCTD 224) and ADYNOVI (eCTD 102).

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

2.3.2. Clinical study

Clinical study number and title

Study 060902: ADVATE/ADYNOVI Haemophilia A Outcome Database (AHEAD)

Description

Study 060902 was an 11-year, single-arm, prospective, non-interventional study (NIS) conducted at 36 sites in Germany and aimed to extend experience from previous clinical studies. The goal of this NIS was to document and compare long-term outcomes of patients receiving ADVATE or ADYNOVI in routine clinical practice (i.e. in accordance with the German label) in terms of quality of life (QoL), haemophilia related co-morbidity, drug utilization, effectiveness, and safety. First patient recruitment was on 07 Jun 2010 and last-patient-out (LPO) was on 31 Mar 2022.

With protocol amendment 5 (24 April 2018) the study was opened to patients receiving treatment with ADYNOVI. Patients, who were already enrolled and treated with ADVATE in the study, could switch from ADVATE to ADYNOVI and were not regarded as new patients.

The planned participation period for patients receiving ADVATE was approximately 8 years from the date of the baseline visit, 4 years for patients treated with ADYNOVI, and 12 years for patients switching from ADVATE to ADYNOVI, unless prematurely discontinued.

The study was closed three years earlier than planned at the sponsor’s decision because of low retention of enrolled patients leading to reduced observation times (up to 10.7 years [3,903 days] for patients receiving ADVATE, up to 3.8 years [1,373 days] for patients receiving ADYNOVI, and up to 11.4 years [4,148 days] for switchers).

Methods

Study participants

The study included patients who had moderate or severe haemophilia A (baseline FVIII ≤5%), who received treatment with ADVATE or ADYNOVI irrespective of purpose or regimen, at the discretion of the reporting physician, and provided a written informed consent. For ADYNOVI, patients were ≥12 years of age.

Treatments

ADVATE and ADYNOVI were prescribed in the usual manner in accordance with the terms of their marketing authorization. The assignment of the patient to a particular therapeutic strategy was not decided by the study protocol but fell within current practice.

Objective(s)

The primary objective of the study was to determine joint health outcome in patients receiving ADVATE or ADYNOVI.

Secondary efficacy objectives included the determination of:

- QoL in patients receiving ADVATE or ADYNOVI
- Haemostatic effectiveness of ADVATE and ADYNOVI in a variety of clinical settings including on-demand therapy, routine standard prophylaxis, and individual PK-guided prophylactic therapy

Outcomes/endpoints

Primary Endpoint

- Incidence of haemophilia-affected joint arthropathy by imaging techniques (e.g. Magnetic Resonance Imaging [MRI], X-ray, ultrasound) and by assessment of the treating physician using only the pain, bleeding, and physical exam parameter of the Gilbert Scale.

Secondary Endpoints

- Incidence of joint replacement therapies
- Incidence of target joint operations
- Incidence of pseudo-tumour development
- Pain associated with bleeding event according to Visual Analog Scale (VAS)-Score
- Quality of life (QoL) using the Haemo-QoL, SF-10TM, SF-12v2TM and Haem-A-QoL questionnaires
- Annualized bleed rate
- Haemostatic effectiveness rating of bleeding episodes treated with ADVATE or ADYNOVI
- Number of units required for bleed resolution
- Number of infusions required for bleed resolution
- Number of days off from school or work due to haemophilia A bleeding episodes
- Incidence of inhibitors in previously treated patients (PTPs): number of FVIII exposure days (EDs) had to be≥5 at baseline visit
- Incidence of inhibitors in minimally treated patients (MTPs): FVIII EDs between 1-4 prior to baseline visit

- Incidence of inhibitors in previously untreated patients (PUPs): naïve to FVIII exposure, FVIII EDs had to be 0 at baseline visit
- Incidence of inhibitors after switching to ADYNOVI
- Incidence of treatment-related serious AEs
- Incidence of treatment-related non-serious AEs
- Compliance with the dosing prescribed and its relationship with effectiveness in prophylaxis regimen
- Modalities of switching from a standard FVIII product to ADYNOVI (prophylaxis regimen)
    - Difference in number of weekly prophylactic infusions between previous regimen and ADYNOVI
    - Difference in number of weekly doses between previous regimen and ADYNOVI
- Status of joint health using the Haemophilia Joint Health Score (HJHS) in patients on ADYNOVI

Sample size

No formal sample size calculation was performed for the determination of the number of patients for documentation. The targeted sample size of 450 patients was based on practical considerations.

Randomisation and blinding (masking)

Not applicable. Study 060902 was a non-interventional study.

Statistical Methods

Continuous variables were summarized using the following descriptive statistics: n, mean, median, standard deviation, Q25, Q75, minimum, maximum. Categorical and count variables were summarized by the number of patients (n) and the percent of patients in each category. Percentages were presented as whole numbers with one decimal point.

Analysis sets

All Patients Set: A patient who was given a patient identification number, and signed the Informed Consent was considered to be enrolled in the study (All Patients Set).

The Safety Analysis: The Safety Analysis (SA) Set included all patients enrolled in the study who have received at least 1 dose of ADVATE/ ADYNOVI since study enrolment.

Switcher Set: The patients who were included the SA Set and switched a treatment from ADVATE to ADYNOVI during the study were included in the Switcher Set.

Subgroup Analyses

Haemophilia severity grading at baseline

- moderate: 1% ≤FVIII ≤5%
- severe: FVIII <1%

Subgroups by the annual visit-specific age

- Paediatric (0 to <12 years)
- Adolescents (12 to <18 years)
- Adults (≥18 years)

Subgroup by FVIII mutation genotype

- Intron-22-inversion
- Large/small deletion/small insertion

- All other mutations

Subgroup by inhibitor history at baseline

- History of inhibitor
- No inhibitor history
- Unknown inhibitor history

Results

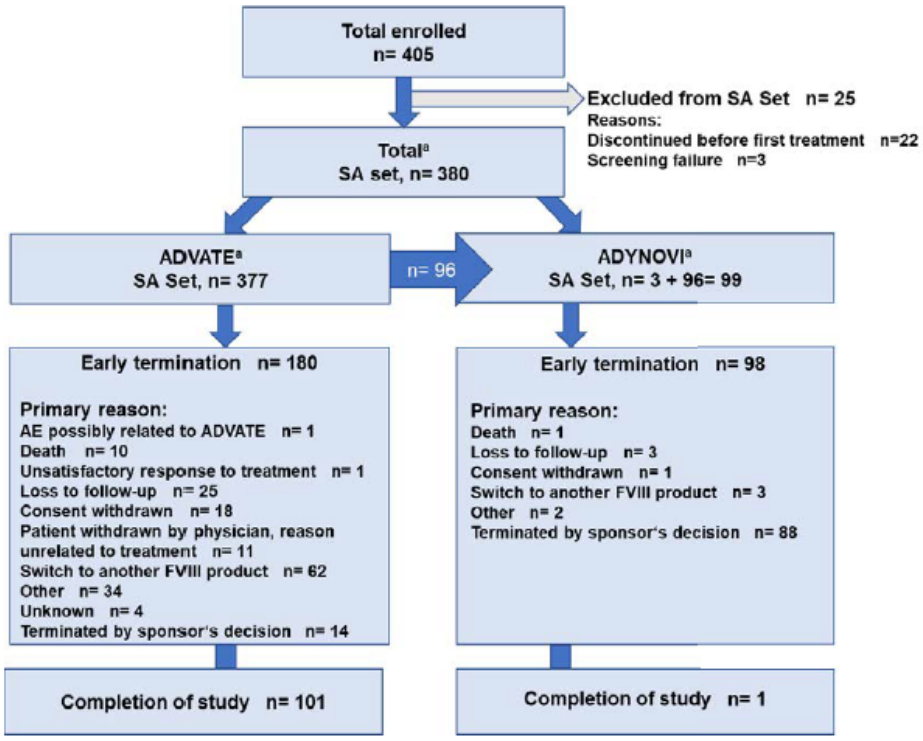
Recruitment/Participant flow/Number analysed

Four hundred and five patients were enrolled at 36 sites in Germany. Data from 380 patients were analysed. They received at least one dose of ADVATE/ADYNOVI since enrolment and constituted the Safety Analysis Set (SA Set). Single sites recruited between 1 and 124 patients.

Of the 405 enrolled patients, 25 were excluded from the analysis because of screening failure (3 patients) or discontinuation before first treatment (22 patients).

Of the 377 patients treated with ADVATE, 180 patients terminated the study early and 101 patients completed the study. Three patients started the study with ADYNOVI and 96 patients switched during the study from treatment with ADVATE to treatment with ADYNOVI. Of 99 ADYNOVI-treated patients, 98 patients terminated the study early (88 out of 98 patients terminated the study due to the sponsor’s decision) and 1 patient completed the study (Figure 1).

Figure 1: Patient disposition



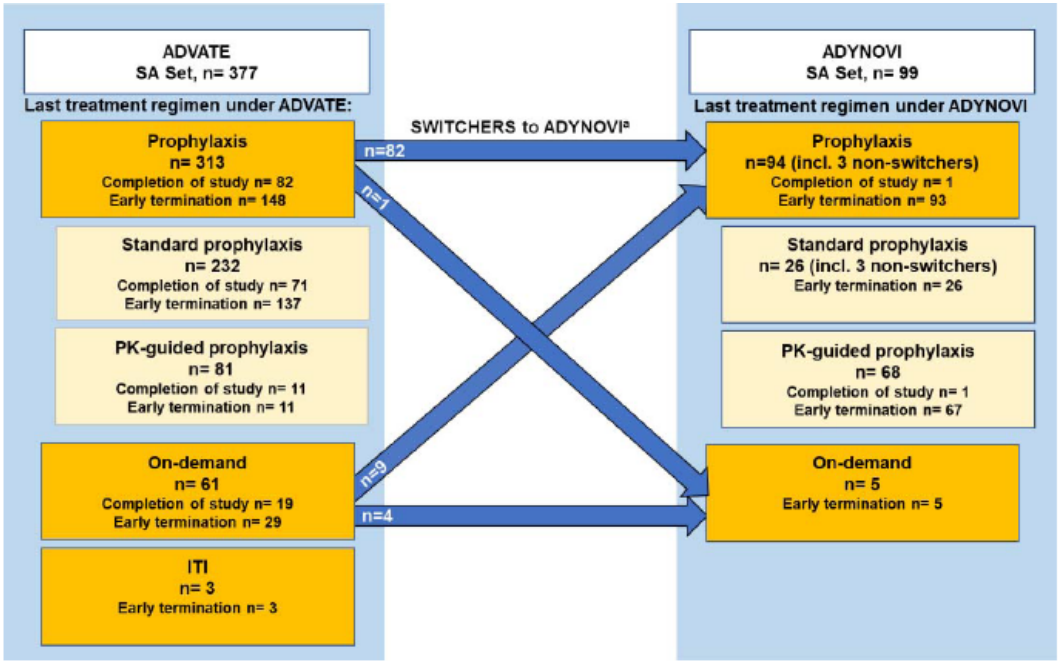
Source table 14.01.02.01. [a]Switchers from ADVATE to ADYNOVI are included in both treatment groups but counted only once in under "Total". 96 patients switched during the study from ADVATE to ADYNOVI treatment, increasing the number of ADYNOVI-treated patients from 3 to 99. The SA Set includes all patients that received at least one dose of ADVATE/ ADYNOVI since study enrollment. AE= Adverse Event, FVIII= Factor VIII, n= number, SA Set= Safety Analysis Set.

Source: Figure 1_clincial study report

Recruitment was temporarily stopped in June 2016 and opened again after implementation of Protocol Amendment 5. During this second recruitment phase, patients treated with ADYNOVI were enrolled starting from January 2018, with recruitment ending on 10 Dec 2021. Patients, who were already enrolled and treated with ADVATE in the study, could switch from ADVATE to ADYNOVI and were not regarded as new patients. These patients continued study documentation with the same patient identification code.

Of 377 ADVATE-treated patients, 313 used ADVATE for prophylaxis. Of these, 232 patients were treated by standard prophylaxis and 81 patients by PK-guided prophylaxis. Sixty-one patients were treated with ADVATE on-demand and 3 patients underwent immune tolerance induction (ITI) (Figure 2).

Figure 2: Patient Disposition in Treatment Regimen Subgroups



Source: Extract of Figure 2_clincial study report

Baseline data

Patients treated with ADVATE had a mean age of 27.5 (SD 17.9) years, were male and mainly Caucasian. Two hundred fifty-two of the 377 (66.8%) patients treated with ADVATE were adults and 74/377 (19.6%) were children aged 2 to <12 years. Thirty six of 377 (9.5%) patients were adolescents aged 12 to <18 years, and 15/377 (4.0%) patients were infants with an age under 2 years (Table 1).

Eighty eight of the 99 (88.9%) patients treated with ADYNOVI were adults and 11/99 (11.1%) were adolescents aged 12 to <18 years.

At baseline, ADVATE was mainly used for prophylaxis across all age subgroups, but also on-demand in adults, children and adolescents and for Immune Tolerance Induction in children and infants. ADYNOVI was used at baseline in adults and adolescents mainly for prophylaxis but also on-demand.

Table 1: Demographic and Baseline Characteristics

	Treatment Regimen at Baseline: ADVATE				Treatment Regimen at Baseline: ADYNOVI			
	Total (N=377)	**Prophylaxis (N=300)**	**On-demand (N=71)**	**ITI (N=6)**	**Total (N=99)**	**Prophylaxis (N=92)**	**On-demand (N=7)**	**ITI (N=0)**
Age [years]								
n (missing)	377 (0)	300 (0)	71 (0)	6 (0)	99 (0)	92 (0)	7 (0)	-
Mean (SD)	27.5 (17.9)	25.4 (17.1)	38.6 (16.4)	3.0 (1.8)	39.1 (15.2)	38.8 (15.2)	43.1 (15.7)	-
Age classes, n (%)								
Infants (age 0 to <2 years)	15 (4.0%)	14 (4.7%)	0 (0.0%)	1 (16.7%)	NA	NA	NA	NA
Children (age 2 to <12 years)	74 (19.6%)	63 (21.0%)	6 (8.5%)	5 (83.3%)	NA	NA	NA	NA
Adolescents (age 12 to <18 years)	36 (9.5%)	35 (11.7%)	1 (1.4%)	0 (0.0%)	11 (11.1%)	10 (10.9%)	1 (14.3%)	-
Adults (age 18 years or older)	252 (66.8%)	188 (62.7%)	64 (90.1%)	0 (0.0%)	88 (88.9%)	82 (89.1%)	6 (85.7%)	-

Source: Extract of Table 1_ Clinical Overview Addendum

The haemophilia grading at screening was severe with FVIII <1% for 82% of both cohorts (ADVATE: 82.0%, ADYNOVI: 82.8%). The majority of these patients was on prophylaxis treatment (ADVATE: 90.0%, ADYNOVI: 87.0%), whereas on-demand treatment was rather used by patients with a moderate Haemophilia grading of ≥1% to ≤5% (ADVATE: 53.5%, ADYNOVI: 71.4%).

Over 84% patients had >150 EDs to ADVATE before study entry. On average, patients used before the study 1,590.0 (SD 765.3) IU of ADVATE per infusion, corresponding to 29.3 (15.5) IU/kg. The average weekly dosage was 5,107.6 (3,174.5) IU, corresponding to 101.9 IU/kg of ADVATE per week.

At baseline, 161/377 (42.7%) of ADVATE-treated patients had documented target joints (i.e. joints with recurrent bleeding episodes). The most frequently affected joints were ankles on both sides, left knee, elbows on both sides and right knee. Per patient, on average 3.2 target joints were documented at baseline (median 2.0). 48/377 (12.7%) patients had had surgical procedures at joints other than joint replacement therapy at 70 target joints. At baseline, 4 (1.3%) patients in the ADVATE prophylaxis group but none in the ADVATE on demand treatment subgroup or in the ADYNOVI treatment group had pseudo-tumours (i.e. encapsulated progressive cystic swellings usually involving muscle and/or bone).

Sixteen of 377 patients in the ADVATE group, but none in the ADYNOVI group reported a history of low or high positive FVIII inhibitor titer in the 24 months before study treatment. Two of 377 (0.6%) patients in the ADVATE group had a high FVIII inhibitor titer >5 BU/ml and 3/377 (0.9%) had a low inhibitor titer (≤5 BU/ml and ≥local cut-off or 0.6 BU/ml), at the last inhibitor test before study treatment.

Efficacy results

Joint health

Data on Gilbert scores were available only for a fraction of patients because documentation of the respective data in a NIS follows routine practice, not a predetermined mandatory schedule. Joint health of all joints with respect to Gilbert scores in ADVATE-treated patients in the prophylaxis and on-demand groups trended toward a numerical decrease (improvement) over time and at last observation after the baseline in the prophylaxis and on-demand groups (Table 2). Gilbert scores in ADYNOVI-treated patients and in treatment groups by prophylaxis type were not further analysed due to limited data available.

Table 2: Average Gilbert Score of All Joints at Baseline, per Study Year, and at Last Observation per Treatment Regimen

		Treatment regimen at baseline	
		ADVATE	
		Prophylaxis	On-demand
Average Gilbert Score (all joints)			
		(N=300)	(N=71)
Baseline	n (missing)	135 (165)	32 (39)
	Mean (SD)	1.8 (2.1)	2.1 (2.8)
	Median	0.8	0.9
	25Q - 75Q	0.3 - 2.8	0.3 - 2.5
		(N=294)	(N=64)
Year 1	n (missing)	83 (211)	16 (48)
	Mean (SD)	1.74 (1.85)	1.69 (2.17)
	Median	1.00	1.08
	25Q - 75Q	0.33 - 2.67	0.33 - 2.25
		(N=281)	(N=60)
Year 2	n (missing)	77 (204)	19 (41)
	Mean (SD)	1.86 (2.00)	1.18 (1.20)
	Median	1.00	0.67
	25Q - 75Q	0.33 - 3.17	0.33 - 1.50
		(N=267)	(N=55)
Year 3	n (missing)	54 (213)	12 (43)
	Mean (SD)	1.57 (1.84)	1.22 (1.12)
	Median	0.67	0.75
	25Q - 75Q	0.33 - 2.67	0.33 - 2.17
		(N=257)	(N=54)
Year 4	n (missing)	38 (219)	8 (46)
	Mean (SD)	1.26 (1.41)	0.58 (0.77)
	Median	0.67	0.33
	25Q - 75Q	0.33 - 1.67	0.08 - 0.75
		(N=224)	(N=48)
Year 5	n (missing)	29 (195)	8 (40)
	Mean (SD)	0.97 (1.07)	0.65 (0.66)
	Median	0.33	0.42
	25Q - 75Q	0.33 - 1.67	0.33 - 0.75
		(N=206)	(N=44)
Year 6	n (missing)	25 (181)	3 (41)
	Mean (SD)	0.68 (0.73)	0.78 (0.69)
	Median	0.33	1.00
	25Q - 75Q	0.33 - 0.83	0.00 - 1.33
		(N=129)	(N=30)
Last observation	n (missing)	129 (0)	30 (0)
	Mean (SD)	1.59 (1.82)	1.16 (1.65)
	Median	0.83	0.67
	25Q - 75Q	0.33 - 2.00	0.33 - 1.33

Source tables 14.02.03.01.02.t and 14.02.03.02.01.t. No total scores were calculated per study year.
25Q - 75Q = 25 quartile - 75 quartile; n/N = patient number; SD = standard deviation.

Source: Table 10_Clinical Study Report

The mean and median maximum and average Gilbert scores were also analysed by prophylaxis type (standard prophylaxis vs PK-guided prophylaxis). However, sample sizes were too limited in PK-guided prophylaxis group to interpret the results. The Patterson score was also not analysed because of a small sample size. After the baseline visit, data were available for only 2 ADVATE-treated patients. Additionally, no data were available for the Haemophilia Joint Health Score.

A higher proportion of patients treated with ADVATE on-demand than for prophylaxis developed new arthropathies during the study (13/80 [16.3%] vs. 37/324 [11.4%]). This applies also to patients with pre-existing target joints in the two ADVATE treatment regimen groups (on demand: 7/37 [18.9%] vs. prophylaxis: 17/124 [13.7%]). Patients undergoing on-demand ADVATE treatment also experienced a higher mean and median number of new arthropathies during the study (mean: on-demand 1.85 vs. prophylaxis 1.41; median: on-demand 2.0 vs. prophylaxis 1.0). In patients treated with ADYNOVI for prophylaxis, 3 patients experienced new arthropathies during the study (Table 3).

Table 3: Summary of Documented New Arthropathies during the Study by Treatment Regimen

	Treatment regimen at baseline			
	ADVATE		ADYNOVI	
	Prophylaxis (N=324)	On-demand (N=80)	Prophylaxis (N=94)	On-demand (N=8)
Patients with documented new arthropathies				
n (%)	37 (11.4%)	13 (16.3%)	3 (3.2%)	-
Patients with pre-existing target joint				
n	124	37	1	-
Patients with pre-existing target joint that developed new arthropathies[a]				
n/n (%)	17/124 (13.7%)	7/37 (18.9%)	-	-
Total number of documented new arthropathies per patient				
n	37	13	3	-
Mean (SD)	1.41 (0.80)	1.85 (0.99)	1.00 (0.00)	-
Median	1.00	2.00	1.00	-
Min - Max	1.0 - 5.0	1.0 - 4.0	1.0 - 1.0	-
Categorized total number of documented new arthropathies per patients				
1	26	6	3	-
2	9	4	-	-
3	1	2	-	-
4	-	1	-	-
5	1	-	-	-
Annualized number of documented new arthropathies per patients				
n	37	13	3	-
Mean (SD)	0.35 (0.64)	0.32 (0.15)	0.39 (0.06)	-
Median	0.18	0.31	0.42	-
Min - Max	0.1 - 4.0	0.1 - 0.7	0.3 - 0.4	-

Max=maximal, Min=minimal, N or n=patient number, SD=standard deviation

[a] Percentage was based on number of patients with pre-existing target joint for each treatment regimen.

Source: Table 4_Clinical Overview Addendum

During the study, no new pseudo-tumours were observed in ADVATE-treated patients. One (1.1%) of ADYNOVI-treated patients developed a pseudo-tumour on the right side of the body.

A similar proportion of patients treated with ADVATE for prophylaxis or on demand had surgical procedures at joints (prophylaxis: 27 [8.3%] patients with 35 target joints vs. 5 [6.3%] patients with 8 target joints). In patients treated with ADYNOVI for prophylaxis, 6 (6.4%) patients experienced surgical procedures at 6 target joints. Between 1.3% and 3.2% of ADVATE- and ADYNOVI-treated patients had joint replacement during the study of knee, ankle and hip.

Assessor's comment:

The presentation of joint health outcomes covers the entire study population. To enable an assessment of joint health (and its development during the course of the study) in children, the MAH should provide a separate analysis of the joint health outcomes collected in study participant <18 years of age (i.e. <2 years, 2 to 12 years, 12-18 years of age).

Quality of Life:

In the ADVATE cohort, evaluation using generic QoL questionnaires SF-10 (in children aged 4 to 17 years) and SF-12, Version 2 (in children aged 4 to17 years and adults) showed stable physical health and well-being in children and stable physical and mental health in children and adults during the study. The Immune Tolerance Induction (ITI) group contained not enough patients and data for evaluation. For the ADYNOVI-treated prophylaxis group aged 12 to 17 years no baseline data were available and sample sizes for post-baseline assessments were small, preventing a meaningful interpretation.

Evaluation using the haemophilia-specific questionnaires Haemo-QoL (in children aged 4 to 7 years, children aged 8 to 12 years, and adolescents aged 13 to 16 years) and Haem-A-QoL (in adults) showed stable overall QoL in children and adolescents in the ADVATE prophylaxis subgroups (The on-demand and the ITI groups contained too few patients to be analysable), and of adults in the ADVATE treatment groups and prophylaxis subgroups. Too few data were available for the ADYNOVI groups to allow a meaningful interpretation.

Improvements of single QoL domains were observed in children aged 4 to 7 years on ADVATE prophylaxis treatment relating to bleeds and global health; in children aged 4 to 7 years on ADVATE standard prophylaxis treatment relating to joint bleeds, feeling, and treatment; and in adolescents aged 13 to 16 years on ADVATE prophylaxis treatment relating to participation in sports and school and to their thoughts about their future. Reductions of single QoL domains were observed in children aged 8 to 12 on ADVATE prophylaxis treatment regarding perceived support by their environment, and in adults on ADVATE on-demand treatment relating to family planning.

Haemostatic Effectiveness

The proportions of ADVATE-treated patients with an ABR of 0 during the study up to study year 8 were 31.5% to 48.6% for prophylactic treatment, 31.8% to 48.3% for standard prophylaxis, 10.0% to 35.3% for PK-guided prophylaxis (up to study year 3), and 25.0% to 42.3% for on-demand treatment.

In general, the proportions of patients with zero bleeding episodes were higher under prophylactic ADVATE treatment than with on-demand ADVATE treatment. Higher proportions of patients with zero bleeding episodes for treatment durations from 1 year to 4 years were observed with prophylactic or on-demand ADYNOVI treatment than with prophylactic or on-demand ADVATE treatment.

Patients treated with ADVATE for prophylaxis had a lower mean and median overall ABR than patients with on-demand treatment (mean [SD]: 4.2 [6.1] vs. 9.6 [13.9]; median [25Q 75Q]: 1.9 [0.7 5.0] vs. 4.0 [0.7 12.7]). In patients with severe haemophilia A, a higher effectiveness of prophylactic vs. on demand treatment was indicated by lower mean and median ABRs (mean [SD]: 4.3 [6.4] vs. 16.3 [17.4]; median [25Q 75Q]: 1.8 [0.7 5.0] vs. 10.1 [2.1 24.2]). Mean ABR tended to decrease over time for patients with prophylactic and on-demand ADVATE treatment. Patients with PK-guided prophylaxis compared to standard prophylaxis had lower mean and median ABRs (mean [SD]: 3.0 [4.0] vs. 4.2 [6.3]; median [25Q 75Q]: 1.6 [0.0 4.2] vs. 1.9 [0.7 5.0]).

Patients treated with ADVATE for prophylaxis had a lower mean and median overall AsBR than patients with on-demand treatment (mean [SD]: 3.3 [5.6] vs. 8.4 [13.2]; median [25Q 75Q]: 1.2 [0.3 4.0] vs. 2.2 [0.3 11.4]). PK-guided prophylaxis compared to standard prophylaxis led to lower mean and median AsBRs (mean [SD]: 1.8 [2.8] vs. 3.4 [5.9]; median [25Q 75Q]: 0.2 [0.0 2.8] vs. 1.2 [0.3 3.9]).

The mean and median AsBRs under treatment with ADVATE in infants, children, adolescents and adults are displayed in Table 4 below. The collected data indicate similar mean and median AsBRs under treatment with ADVATE in infants, children, adults and lower mean and median AsBRs in adolescents

(mean [SD]: 3.9 [4.4] vs. 3.3 [6.2] vs. 3.6 [6.1] vs. 2.7 [3.8]; median (25Q 75Q): 1.5 [0.8 6.9] vs. 1.3 [0.5 3.1] vs. 1.2 [0.2 3.9] vs. 1.1 [0.3 2.7]).

Table 4: Total Annualized Spontaneous Bleeding Rate by Treatment Regimen and Prophylaxis Type by Age Group

	Treatment Regimen			
	ADVATE			
	Standard Prophylaxis	PK-guided Prophylaxis	Prophylaxis	On-demand
Overall	**Annualized spontaneous bleeding rate (AsBR) – infants (age 0 to <2 years)**			
N in subgroup	**14**	**1**	**15**	**0**
n (missing)	13 (1)	1 (0)	14 (1)	-
Mean (SD)	3.9 (4.4)	8.4 (.)	4.3 (4.4)	-
Median	1.5	8.4	2.1	-
25Q - 75Q	0.8 - 6.9	8.4 - 8.4	0.8 - 7.6	-
Overall	**AsBR – children (age 2 to <12 years)**			
N in subgroup	**69**	**6**	**70**	**6**
n (missing)	66 (3)	6 (0)	67 (3)	5 (1)
Mean (SD)	3.3 (6.2)	1.4 (2.0)	3.2 (6.1)	1.9 (2.1)
Median	1.3	0.4	1.6	0.8
25Q - 75Q	0.5 - 3.1	0.0 - 3.1	0.5 - 3.5	0.6 - 3.0
Overall	**AsBR – adolescents (age 12 to <18 years)**			
N in subgroup	**35**	**8**	**35**	**4**
n (missing)	35 (0)	7 (1)	35 (0)	4 (0)
Mean (SD)	2.7 (3.8)	0.5 (0.9)	2.6 (3.8)	1.4 (1.2)
Median	1.1	0.0	1.1	1.5
25Q - 75Q	0.3 - 2.7	0.0 - 1.6	0.3 - 2.7	0.4 - 2.4
Overall	**AsBR – adults (age 18 years or older)**			
N in subgroup	**204**	**66**	**204**	**70**
n (missing)	201 (3)	58 (8)	201 (3)	69 (1)
Mean (SD)	3.6 (6.1)	1.9 (2.9)	3.4 (5.8)	9.3 (13.8)
Median	1.2	0.2	1.2	2.4
25Q - 75Q	0.2 - 3.9	0.0 - 3.0	0.2 - 4.0	0.3 - 13.1

Source tables 14.02.04.03.02.16.01.t and 14.02.04.03.02.15.01.t. ABR was set to missing according to 90 days rule. Patients were included in age subgroups according to age at baseline. "PK-guided Prophylaxis" contains patients from MyPKFiT-guided Prophylaxis and the only patient using "Other PK-guided Prophylaxis". 25Q - 75Q= 25-quartile to 75-quartile, AsBR= Annualized spontaneous Bleeding Rate, N or n= number of patients, PK-guided= pharmacokinetics-guided, SD= standard deviation.

Source: Table 53_Clinical Study Report

In patients with treatment for prophylaxis, the total mean and median ABRs were higher during treatment with ADVATE and lower after switching to ADYNOVI (mean (SD) of 3.6 [4.3] vs.1.6 [2.5]; median of 2.2 vs. 0.7). The total AJBR was also higher in the prophylaxis group during treatment with

ADVATE than after switching to ADYNOVI (mean [SD] of 1.9 [3.4] vs. 0.8 ([1.6]; median of 0.9 vs. 0.0). AsBR followed a similar trend with a higher rate observed during ADVATE treatment than after switching to ADYNOVI (mean [SD] of 2.6 [3.9] vs. 0.9 [2.2]; median of 1.3 vs. 0.0).

Table 5: Switching Analysis: ABR in Prophylaxis Regimen – before and after Switching

	Treatment Regimen					
	ADVATE			ADYNOVI		
	Total Prophy-laxis (N=84)	Standard Prophy-laxis (N=84)	PK-guided Prophy-laxis (N=59)	Total Prophy-laxis (N=91)	Standard Prophy-laxis (N=29)	PK-guided Prophy-laxis (N=68)
Total ABR						
n (missing)	84 (0)	84 (0)	55 (4)	88 (3)	28 (1)	63 (5)
Mean (SD)	3.6 (4.3)	3.8 (5.1)	2.9 (3.7)	1.6 (2.5)	1.9 (2.4)	1.4 (2.5)
Median	2.2	2.2	1.9	0.7	1.0	0.7
25Q - 75Q	0.7 - 5.0	0.7 - 4.9	0.0 - 4.2	0.0 - 1.7	0.0 - 3.3	0.0 - 1.7
AJBR						
n (missing)	84 (0)	84 (0)	55 (4)	88 (3)	28 (1)	63 (5)
Mean (SD)	1.9 (3.4)	2.0 (4.0)	1.4 (2.3)	0.8 (1.6)	0.7 (1.2)	0.8 (1.8)
Median	0.9	0.9	0.0	0.0	0.3	0.0
25Q - 75Q	0.1 - 2.2	0.2 - 2.1	0.0 - 1.9	0.0 - 0.8	0.0 - 0.8	0.0 - 0.8
AsBR						
n (missing)	84 (0)	84 (0)	55 (4)	88 (3)	28 (1)	63 (5)
Mean (SD)	2.6 (3.9)	2.8 (4.9)	1.9 (3.0)	0.9 (2.2)	1.0 (1.5)	0.8 (2.4)
Median	1.3	1.3	0.0	0.0	0.4	0.0
25Q - 75Q	0.2 - 4.0	0.3 - 3.8	0.0 - 3.0	0.0 - 0.8	0.0 - 1.2	0.0 - 0.6

Source table14.08.03. "PK-guided Prophylaxis" contains patients from MyPKFiT-guided Prophylaxis and the only patient using "Other PK-guided Prophylaxis". Total Prophylaxis includes the overall Prophylaxis duration. 25Q - 75Q= 25-quartile to 75-quartile, ABR= Annualized Bleeding Rate, AsBR= Annualized severe Bleeding Rate, N or n= number, PK-guided= pharmacokinetics-guided, SD= standard deviation.

Source: Table 74_ Clinical Study Report

For patients with ADVATE treatment, 565 investigator global effectiveness assessments for bleeding episodes were available for prophylactic and 163 for on-demand treatment. In patients treated prophylactically with ADYYNOVI, 7 investigator global effectiveness assessments were available. Investigators and patients rated the global effectiveness of ADVATE prophylactic treatment in 94% and 86.9% of bleeding episodes and on-demand treatment in 99.4% and 94.8% of bleeding episodes as "good" to "excellent." ADYNOVI prophylaxis was rated by investigators in 85.7% of bleeding episodes as "good."

Drug utilisation

The mean annualized weight-adjusted total dose (SD) of ADVATE during the study was 4,921.4 (4,687.9) IU/kg total, 5,359.1 (2,968.2) IU/kg in the prophylaxis group, 625.4 (628.9) IU/kg in the on-demand group. The mean annualized weight-adjusted total dose (SD) for ADYNOVI was 4,643.2 [2,530.3] IU/kg total, 4,776.9 [2,474.6] IU/kg in the prophylaxis group, and 1,235.0 [759.7] IU/kg in the on-demand group. The ADYNOVI-on-demand group had a minimal sample size (n=8) making statistical evaluation inadequate.

In adults, the mean annualized total dose used by adult patients during the study for prophylaxis overall was 321,858.9 [SD 183,478.9] IU for ADVATE and, with 350,804.0 [165,821.1] IU, higher for

ADYNOVI. The mean annualized number of infusions was 167.2 [67.1] for ADVATE and 163.7 [79.4] for ADYNOVI. The mean treatment duration was 1,979.9 [879.6] days for ADVATE and 793.1 [333.2] days for ADYNOVI.

Consumption data obtained in the paediatric subset of the study population are summarized in Table 6 below.

In infants, the mean annualized total dose used during the study for prophylaxis overall was 116,654.2 [SD 69,703.2] IU for ADVATE, reflecting the lower weight of infants compared to adults. The mean annualized number of infusions was 152.0 [35.6] and the mean treatment duration 2,017.1 [892.2] days.

In children, the mean annualized total dose used during the study for prophylaxis overall was 213,214.2 [SD 105,966.7] IU for ADVATE. The mean annualized number of infusions was 166.9 [36.3] and the mean treatment duration 2,326.4 [821.3] days.

In adolescents, the mean annualized total dose used during the study for prophylaxis overall was 295,543.2 [SD 102,921.4] IU for ADVATE and with 324,320.1 [108,669.4] IU higher for ADYNOVI. The mean annualized number of infusions was 166.4 [38.8] for ADVATE and 146.4 [31.0] for ADYNOVI. The mean treatment duration was 2,121.4 [1,027.7] days for ADVATE and 722.5 [428.0] days for ADYNOVI.

Table 6: Overall Factor VIII Administration for Prophylactic Treatment in paediatric study subjects

A

	Treatment regimen		
	ADVATE		
	Standard Prophylaxis (N=14)	PK-guided Prophylaxis (N=1)	Total Prophylaxis (N=15)
Age group at baseline: Infants (0 to <2 years)			
Total dose annualized [IU]			
n (missing)	14 (0)	1 (0)	15 (0)
Mean (SD)	119,716.3 (71,279.7)	73,784.8 (.)	116,654.2 (69,703.2)
Median	97,583.9	73,784.8	94,577.3
25Q - 75Q	65,414.4 - 176,010.6	73,784.8 - 73,784.8	65,414.4 - 176,010.6
Annualized number of infusions			
n (missing)	14 (0)	1 (0)	15 (0)
Mean (SD)	151.7 (36.9)	156.5 (.)	152.0 (35.6)
Median	160.4	156.5	158.8
25Q - 75Q	149.8 -179.0	156.5 -156.5	149.8 -179.0
Treatment duration [days]			
n (missing)	14 (0)	1 (0)	15 (0)
Mean (SD)	2,077.6 (893.4)	1,170.0 (.)	2,017.1 (892.2)
Median	2,030.0	1,170.0	1,874.0
25Q - 75Q	1,494.0 - 2,857.0	1,170.0 - 1,170.0	1,314.0 - 2,857.0
n (%) pts per dose frequency category[a]			
Daily	-	-	-
Every 2 days	9 (64.3%)	-	9 (60.0%)
Every 3 days	2 (14.3%)	-	2 (13.3%)
3 times/wk	12 (85.7%)	1 (100.0%)	13 (86.7%)
2 times/wk	6 (42.9%)	-	6 (40.0%)
Once/wk	4 (28.6%)	-	4 (26.7%)
Other	-	-	-
Twice daily	-	-	-

B

	Treatment regimen		
	ADVATE		
	Standard Prophylaxis (N=69)	PK-guided Prophylaxis (N=6)	Total Prophylaxis (N=70)
Age group at baseline: Children (2 to <12 years)			
Total dose annualized [IU]			
n (missing)	69 (0)	6 (0)	70 (0)
Mean (SD)	213,605.7 (106,045.0)	162,821.0 (76,783.5)	213,214.2 (105,966.7)
Median	180,101.2	156,533.6	177,508.0
25Q - 75Q	134,938.2 - 285,223.9	104,355.7-182,622.5	131,588.3 - 285,223.9
Annualized number of infusions			
n (missing)	69 (0)	6 (0)	70 (0)
Mean (SD)	167.8 (35.2)	156.5 (28.6)	166.9 (36.3)
Median	161.8	156.5	161.5
25Q - 75Q	156.5 - 182.6	156.5 - 182.6	156.5 -182.6
Treatment duration [days]			
n (missing)	69 (0)	6 (0)	70 (0)
Mean (SD)	2,206.8 (832.4)	1,008.0 (422.1)	2,326.4 (821.3)
Median	2,300.0	882.0	2,642.5
25Q - 75Q	1,865.0 – 2,883.0	812.0 -1,363.0	1,996.0 – 2,920.0
n (%) pts per dose frequency category[a]			
Daily	2 (2.9%)	-	2 (2.9%)
Every 2 days	40 (58.0%)	2 (33.3%)	40 (57.1%)
Every 3 days	7 (10.1%)	-	7 (10.0%)
3 times/wk	40 (58.0%)	3 (50.0%)	40 (57.1%)
2 times/wk	6 (8.7%)	1 (16.7%)	7 (10.0%)
Once/wk	4 (5.8%)	-	4 (5.7%)
Other	2 (2.9%)	-	2 (2.9%)
Twice daily	-	-	-

	Treatment regimen					
	ADVATE			ADYNOVI		
	Standard Prophylaxis (N=35)	PK-guided Prophylaxis (N=8)	Total Prophylaxis (N=35)	Standard Prophylaxis (N=2)	PK-guided Prophylaxis (N=8)	Total Prophylaxis (N=10)
Age group at baseline: Adolescents (12 to <18 years)						
Total dose annualized [IU]						
n (missing)	35 (0)	8 (0)	35 (0)	2 (0)	8 (0)	10 (0)
Mean (SD)	295,543.2 (102,921.4)	304,370.8 (73,936.9)	295,543.2 (102,921.4)	268,810.2 (62,055.9)	338,197.6 (116,329.0)	324,320.1 (108,669.4)
Median	305,645.5	339,156.1	305,645.5	268,810.2	313,067.1	312,878.7
25Q - 75Q	234,800.4 - 365,245.0	239,148.5 - 365,245.0	234,800.4 - 365,245.0	224,930.0 - 312,690.3	247,844.8 - 413,614.9	234,800.4 - 365,245.0
Annualized number of infusions						
n (missing)	35 (0)	8 (0)	35 (0)	2 (0)	8 (0)	10 (0)
Mean (SD)	166.4 (38.8)	191.3 (73.5)	166.4 (38.8)	121.6 (0.0)	152.6 (31.9)	146.4 (31.0)
Median	156.5	182.6	156.5	121.6	156.5	156.5
25Q - 75Q	156.5 - 182.6	156.5 - 182.6	156.5 - 182.6	121.6 - 121.6	130.4 - 180.0	121.6 - 177.3
Treatment duration [days]						
n (missing)	35 (0)	8 (0)	35 (0)	2 (0)	8 (0)	10 (0)
Mean (SD)	2,042.5 (989.5)	566.8 (291.9)	2,121.4 (1027.7)	1,200.0 (0.0)	603.1 (392.6)	722.5 (428.0)
Median	2,268.0	612.5	2,590.0	1,200.0	527.5	718.0
25Q - 75Q	978.0 - 3003.0	426.5 - 787.5	978.0 - 3,059.0	1,200.0 -1,200.0	361.5 - 956.0	375.0 - 1,133.0
n (%) patients in dose frequency categories[a]						
Daily	2 (5.7%)	1 (12.5%)	2 (5.7%)	-	-	-
Every 2 days	15 (42.9%)	4 (50.0%)	15 (42.9%)	-	3 (37.5%)	3 (30.0%)
Every 3 days	3 (8.6%)	1 (12.5%)	3 (8.6%)	2 (100.0%)	1 (12.5%)	3 (30.0%)
3 times/wk	24 (68.6%)	2 (25.0%)	24 (68.6%)	-	3 (37.5%)	3 (30.0%)
2 times/wk	3 (8.6%)	-	3 (8.6%)	-	2 (25.0%)	2 (20.0%)
Once/wk	2 (5.7%)	-	2 (5.7%)	-	-	-
As needed	1 (2.9%)	-	1 (2.9%)	-	-	-
Other	1 (2.9%)	-	1 (2.9%)	-	-	-

Source: Tables 67-69_Clinical Study Report

In both treatment regimen groups over 50% of bleeds were treated with one infusion (Table 7). Only a minority of bleeds did not require FVIII infusions. Overall, 0 to 4 infusions and more were used for bleeding cessation. Mean and median dosage per infusion in IU for bleed cessation were comparable in patients treated with ADVATE or ADYNOVI for prophylaxis, the weighted dosage per infusion in IU/kg for bleed cessation was at most slightly lower with ADYNOVI.

Table 7: FVIII Administration for Bleeding Cessation by Treatment Regimen

	Treatment regimen					
	ADVATE			ADYNOVI		
	Total (N=377)	Prophylaxis (N=324)	On-demand (N=80)	Total (N=99)	Prophylaxis (N=94)	On-demand (N=8)
Number of infusions required for bleed cessation						
n (missing)	10,443 (343)	7,316 (260)	3,099 (80)	370 (44)	307 (40)	63 (4)
Mean (SD)	2.8 (5.7)	3.0 (6.2)	2.2 (4.0)	3.9 (9.3)	4.2 (10.0)	2.9 (4.5)
Median	1.0	1.0	1.0	1.0	1.0	1.0
25Q - 75Q	1.0 - 2.0	1.0 - 3.0	1.0 - 2.0	1.0 - 4.0	1.0 - 4.0	1.0 - 2.0
Number of infusions (per bleed) categorized						
0 infusions	7 (0.1%)	3 (0.0%)	4 (0.1%)	-	-	-
1 infusion	6,015 (57.6%)	4,012 (54.8%)	1,996 (64.4%)	202 (54.6%)	164 (53.4%)	38 (60.3%)
2 infusions	1,928 (18.5%)	1,391 (19.0%)	532 (17.2%)	52 (14.1%)	42 (13.7%)	10 (15.9%)
3 infusions	807 (7.7%)	584 (8.0%)	222 (7.2%)	23 (6.2%)	20 (6.5%)	3 (4.8%)
≥4 infusions	1,686 (16.1%)	1,326 (18.1%)	345 (11.1%)	93 (25.1%)	81 (26.4%)	12 (19.0%)
Missing	343	260	80	44	40	4
Weighted dosage per infusion [IU/kg]						
n (missing)	372 (5)	317 (7)	78 (2)	95 (4)	90 (4)	7 (1)
Mean (SD)	34.3 (31.4)	34.4 (32.0)	27.8 (13.1)	30.6 (54.9)	30.5 (56.2)	23.6 (24.4)
Median	31.6	31.5	28.4	25.6	25.6	24.9
25Q - 75Q	25.0 - 39.4	25.1 - 39.9	23.0 - 35.6	0.0 - 38.9	0.0 - 38.8	0.0 - 50.5

Source: Extract of Table 61_Clinical Study Report

Safety results

The overall study duration (SD) was 2,363.9 (825.7) days or 6.5 (2.3) years for patients treated with ADVATE and 988.3 (283.2) days or 2.7 (0.8) years for patients treated with ADYNOVI.

A total of 2,153 AEs were reported for 318 (84.4%) patients in the ADVATE cohort and 217 AEs for 66 (66.7%) patients in the ADYNOVI cohort. The lower frequency of AEs in the ADYNOVI cohort can be attributed to the shorter observation time on ADYNOVI than ADVATE treatment. The incidence of AEs per 100 patient years was only slightly smaller with 94.4 in the ADVATE cohort than with 100.9 in the ADYNOVI cohort. The severity of most AEs was mild or moderate.

With 145 of 2,153 AEs affecting 92 (24.4%) patients in the ADVATE cohort and 15 of 217 AEs affecting 10 (10.1%) patients in the ADYNOVI cohort, below 10% of AEs were rated as severe.

AEs leading to study discontinuation occurred in 7 (1.9%) patients in the ADVATE cohort, thereof 6 (1.9%) patients in the prophylaxis and 1 (1.3%) patient in the on-demand treatment group. During the whole observation period no treatment-related AE led to study discontinuation.

A total of 39 treatment-related AEs were reported for 20 (5.3%) patients in the ADVATE cohort and 7 treatment-related AEs for 5 (5.1%) patients in the ADYNOVI cohort. In the ADVATE cohort, for 3 patients each, "Haemorrhage" and "Factor VIII inhibition" were reported as treatment-related AEs and, for 2 patients each, "Contusion", "Fall" and "Haemarthrosis". The remaining 27 treatment-related events were single occurrences in 14 SOCs with 5 AEs in the SOC "Nervous System Disorders", 4 AEs each in the SOCs "Injury, poisoning and procedural complications", and "Gastrointestinal disorders", and 3 AEs each in the SOCs "Musculoskeletal and connective tissue disorders", "General disorders and administration site conditions", and "Skin and subcutaneous tissue disorders." The 7 treatment-related AEs in the ADYNOVI cohort were "Vertigo", "Intra-abdominal haemorrhage", "Drug ineffective", "Synovitis", "Epilepsy", "Depression", and "Sleep disorder." No treatment-related AE led to study discontinuation.

Serious AEs (SAEs) were documented for 156 (41.4%) patients in the ADVATE and 26 (26.3%) patients in the ADYNOVI cohort. 35 treatment-related SAEs were reported for 16 (4.2%) patients and in the ADYNOVI cohort 4 treatment-related SAEs for 4 (4.0%) patients. One patient on ADVATE prophylaxis treatment experienced an SAE leading to death.

Assessor's comment:

Some of the treatment-related (S)AEs reported in study 060902 (as summarized in source tables 14.04.05.t and 14.04.05.v) are currently not mentioned in section 4.8 of the ADVATE/ADYNOVI SmPCs. Consequently, the MAH's claim that there is no need to update the respective PIs requires further justification. The reported cases of treatment-related hepatitis C, epilepsy, jugular vein thrombosis and acute myocardial infarction are considered particularly noteworthy and should be further discussed on the basis of additional information.

The reported case of a fatal SAE affected a study subject (unknown sex or race with a weight of and a height of), who received ADVATE (500 IU i.v., three times per week) for haemophilia A prophylaxis since 2006 onwards. The patient received several concomitant treatments for pain (Cox-2 inhibitor etericoxib on, the opioid tramadol in, fentanyl tablets in) and the antidepressant amitryptiline in. The indication for these comedications is unknown. The emergency physician who responded to the death documented the cause of death as unknown. The subject's general physician suspected death was due to an. No autopsy was performed and the cause of death could not be substantiated.

Noteworthy, listing 16.02.04.02 lists the fatal SAE as 'related'. However, as explained by the applicant, this entry resulted from the restriction to binary entries, i.e. 'related' or 'not related'. The reporter assessed the death as 'unlikely related' and the Sponsor assessed the event as 'not related' to ADVATE.

Subgroup Analyses by Age Group

For the age group 0 to <2 years, 15 infants and for the age group 2 to <12 years, 74 children were included in the ADVATE cohort. In both age groups about 87% of patients experienced AEs and about 40% had SAEs. For children the incidence of AEs per 100 patient years was 318.5 under the on-demand treatment and only 119.4 under prophylaxis treatment. For infants and children, no (S)AE leading to death occurred.

Assessor's comment

The presentation of treatment-related (S)AEs reported in study 060902 covers the entire study population. To enable an assessment of safety in the paediatric subset, the MAH should provide separate presentations of treatment-related (S)AEs reported in study participant <18 years of age (i.e. <2 years, 2 to 12 years, 12-18 years of age) and critically discuss potential age-related differences.

Inhibitor Development During the Study

During the study, eight of 354 (2.3%) patients undergoing ADVATE treatment had a positive titer for neutralizing antibodies against FVIII according to local cut-off or ≥0.6 BU/ml. In two of 354 (0.6%) patients inhibitor titers were high (>5 BU/ml). No inhibitors were observed in patients treated with ADYNOVI.

De novo inhibitor development (i.e. at least two positive inhibitor measurements per patient during the study [titer ≥0.6 BU or confirmed positive] and no historical titer ≥0.6 BU or positive inhibitor titer screening visit), was observed in one patient with on-demand ADVATE treatment but not in patients with prophylactic ADVATE treatment.

No inhibitors were observed after switching from ADVATE to ADYNOVI.

Assessor's comment

According to the respective narrative, the reported de novo inhibitor development affected a male with >150 ED before the study. This subject also experienced concurrent autoimmune disorders (Lupus anticoagulants antibodies, anti-phospholipid syndrome). The patient received a total dose of 1153.92 IU/kg corresponding to 18 EDs during the study. The patient showed low positive inhibitor titers (1.11 to 2.97 BU/ml) and FVIII plasma levels remained within the targeted range. No action was taken and no causality was documented. The patient continued treatment with ADVATE or ADYNOVI (not further specified) after he left the study in.

2.3.3. Discussion on clinical aspects

As part of this Article 46 procedure, the MAH submitted the final report of study 060902 together with an updated Critical Expert Overview. Study 060902 was an 11-year, single-arm, prospective, non-interventional study (NIS) conducted at 36 sites in Germany with the goal to document and compare long-term outcomes (in terms of QoL, haemophilia-related co-morbidity, drug utilization, effectiveness, and safety) of patients receiving ADVATE or ADYNOVI in routine clinical practice.

Data was collected between June 2010 and March 2022, with ADYNOVI treated patients (>12 years of age) being included since April 2018. Patients, who were already enrolled and treated with ADVATE in the study could switch from ADVATE to ADYNOVI.

The overall study duration (SD) was 2,363.9 (825.7) days or 6.5 (2.3) years for patients treated with ADVATE and 988.3 (283.2) days or 2.7 (0.8) years for patients treated with ADYNOVI.

The study analysed real-world data from a total of 380 patients with moderate or severe haemophilia A including a subset of paediatric subjects who received ADVATE (n=15 infants aged <2years, n=74 children aged 2 to <12 years, n=36 adolescents) or ADYNOVI (n=11 adolescents) for on demand or prophylactic treatment according to daily clinical practice and patient needs.

In essence, results of study 060902 complement the findings from previous clinical trials and provide additional support for an effective and well-tolerated use of ADVATE and ADYNOVI in the treatment of haemophilia A under real-world conditions (i.e. in daily clinical practice).

Joint health and bleeding data indicate low ABRs under treatment, effectiveness in the treatment of bleeding episodes, low numbers of disease-related complications (i.e. new arthropathies or pseudo-tumours) and maintained QoL. In addition, consumption data indicate application frequencies consistent with the approved posologies (i.e. every 2-3 days for ADVATE and every 3-4 days for ADYNOVI) with only few exceptions.

According to the applicant, switching from ADVATE to ADYNOVI resulted in fewer bleeding episodes per year, despite a shift towards reduced dose frequencies (but comparable annualised consumption) consistent with the reported prolonged half-life of ADYNOVI.

However, interpretation of these comparative analyses is severely hampered by the study's non-interventional design with i) a huge proportion of missing information due to non-mandatory documentation, ii) substantial differences in group sizes and follow-up durations, iii) age imbalances due to ADYNOVI's restricted indication to patients ≥12 years of age, and iv) likely bias arising from a successive enrichment of favourable responders during the course of the study.

As noted by the applicant, the number of treatment-related AEs observed in study 060902 with ADVATE was lower than the ADRs observed in clinical studies (39 events per 377 patients vs. 93 ADRs per 418 patients) and the proportion of patients affected by treatment-related AEs with ADYNOVI was the same as observed in the Phase 3b Continuation study in PTPs with severe haemophilia A (5.1%).

However, some of the treatment-related (S)AEs reported in study 060902 (as summarized in source tables 14.04.05.t and 14.04.05.v) are currently not mentioned in section 4.8 of the ADVATE/ADYNOVI SmPCs. Therefore, the MAH's claim that there is no need to update the respective PIs requires further justification. The reported cases of treatment-related hepatitis C, epilepsy, jugular vein thrombosis and acute myocardial infarction are considered particularly noteworthy and should be further discussed on the basis of additional information.

Proportions of patients experiencing AEs under prophylactic treatment were comparable over all age groups studied. However, the presentation of treatment-related (S)AEs is limited to the entire study population. Hence, to enable an assessment of potential age-related differences, the MAH should provide separate presentations of treatment-related (S)AEs reported in the paediatric subset of the study population (i.e. <2 years, 2 to 12 years, 12-18 years).

3. Rapporteur's overall conclusion and recommendation

In summary, the real-world data collected in study 060902 do not change the favourable benefit-risk profile of ADVATE and ADYNOVI in their approved indications. The presented data do not warrant any update of their Product informations 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. The MAH should provide additional information on the definition of PK-guided prophylactic treatment, including information on the targeted trough levels.

2. The presentation of joint health outcomes and haemophilia-related co-morbidity obtained in study 060902 covers the entire study population. To enable an assessment of joint health (and its development during the course of the study) in the paediatric subset, the MAH should provide a separate analysis of study outcomes collected in participants <18 years of age (i.e. <2 years, 2 to 12 years, 12-18 years).

3. Some of the treatment-related (S)AEs reported in study 060902 (as summarized in source tables 14.04.05.t and 14.04.05.v) are currently not mentioned in section 4.8 of the ADVATE/ADYNOVI SmPCs. Consequently, the MAH's claim that there is no need to update the Product Informations requires further justification. The reported cases of treatment-related hepatitis C, epilepsy, jugular vein thrombosis and acute myocardial infarction are considered particularly noteworthy and should be further discussed on the basis of additional information.

4. The presentation of treatment-related (S)AEs reported in study 060902 covers the entire study population. To enable an assessment of safety in the paediatric subset, the MAH should provide separate presentations of treatment-related (S)AEs reported in study participant <18 years of age (i.e. <2 years, 2 to 12 years, 12-18 years) and critically discuss potential age-related differences.

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

5. MAH responses to Request for supplementary information

Question 1

The MAH should provide additional information on the definition of PK-guided prophylactic treatment, including information on the targeted trough levels.

Summary of the Applicant's Response

Within the AHEAD Germany study, a prophylaxis regimen using individual PK characteristics to guide the dose could be employed to maintain factor VIII (FVIII) trough levels ≥1% above baseline at 72-hour intervals, as described by Valentino et al (Valentino et al. 2012).

The prophylaxis regimen included:

- Standard prophylaxis
- MyPKFit-guided prophylaxis (software used for PK-based assessment: myPKFit)
- Other PK software–guided prophylaxis (software used for PK-based assessment: NONMEN, SAS, TCIWorks, WAPPS, WinNonLin, other, unknown)

The utility of prophylaxis dose tailoring with individual PK (dose-exposure responses) is focused on optimizing treatment efficacy, safety, and FVIII usage through individualized dosing levels and frequencies supported by software such as myPKFit and other marketed tools.

Valentino, L. A., Mamonov, V., Hellmann, A., Quon, D. V., Chybicka, A., Schroth, P., et al. 2012. A randomized comparison of two prophylaxis regimens and a paired comparison of on-demand and prophylaxis treatments in hemophilia A management. J. Thromb. Haemost, 10(3), 359-67.

Assessment of the Applicant's Response

As requested, the MAH provided additional information on the definition of PK-guided prophylactic treatment in study 060902. According to the MAH's response, PK-tailored prophylactic treatment targeted trough levels ≥1% above baseline at 72-hour intervals. As such, PK-guided treatment essentially followed the approach studied and published by Valentino et al. in 2012, which is also reflected in section 5.1 of the ADVATE SmPC.

Conclusion

Issue resolved.

Question 2

The presentation of joint health outcomes and haemophilia-related co-morbidity obtained in study 060902 covers the entire study population. To enable an assessment of joint health (and its development during the course of the study) in the paediatric subset, the MAH should provide a separate analysis of study outcomes collected in participants <18 years of age (i.e. <2 years, 2 to 12 years, 12-18 years).

Summary of the Applicant's Response

A separate analysis of study outcomes collected in participants by age group at baseline or visit specific categorized as 0 to <2, 2 to <12, 12 to <18, and≥18 years is provided in *EMA Tables – Joint Health and EMA Figures – Joint Health*. Results from this analysis are summarized below.

There were no Gilbert Scores collected for patients aged under 2 years. For the ADYNOVI arm, a Gilbert score was collected for 1 adolescent patient at Study Year 1 (average score=0.33). There are no Gilbert score data for the immune tolerance induction (ITI) regimen for either ADVATE or ADYNOVI.

Eleven (11, 10 in prophylaxis and 1 in on-demand) patients in the ADYNOVI arm, who were aged 12 to <18 years, had no new arthropathies documented. For patients who were aged under 18 years, no joint operations occurred during the study for the ADYNOVI arm.

For patients who were aged under 18 years, no pseudo-tumours and no joint replacement therapies occurred during the study for both the ADVATE and ADYNOVI arms.

Table 1 Summary of Documented New Arthropathies During the Study by Age Group (SA Set)

Treatment Arm[a]	Treatment Regimen[a]	Age Groups (Years) 0-<2 (N=15)	2-<12 (N=74)	12-<18 (N=36)	≥18 (N=252)
ADVATE					
Number of patients with pre-existing target joint					
		n	n	n	n
	Prophylaxis	-	-	5	119
	On-demand	-	-	-	37
	ITI	-	-	-	-
Number (%) of patients with documented new arthropathies during the study					
		N, n (%)	N, n (%)	N, n (%)	N, n (%)
	Prophylaxis	15, -	70, 5 (7.1)	35, 5 (14.3)	204, 27 (13.2)
	On-demand	0, -	6, -	4, -	70, 13 (18.6)
	ITI	2, -	6, -	0, -	1, -
Number (%) of patients with pre-existing target joint developed documented new arthropathies during study[b]					
		n (%)	n (%)	n (%)	n (%)
	Prophylaxis	NA	-	-	17 (14.3)
	On-demand	NA	-	-	7 (18.9)
	ITI	NA	-	-	-
Total number of documented new arthropathies per patients during study					
	Prophylaxis				
	n, Mean (SD)	NA	5, 1.4 (0.55)	5, 1.4 (0.89)	27, 1.4 (0.84)
	Median (Min, Max)	NA	1.0 (1.0, 2.0)	1.0 (1.0, 3.0)	1.0 (1.0, 5.0)
	On-demand				
	n, Mean (SD)	NA	-	-	13, 1.9 (0.99)
	Median (Min, Max)	NA	-	-	2.0 (1.0, 4.0)
	ITI	NA	-	-	-
Annualized number of documented new arthropathies per patients during the study					
	Prophylaxis				
	n, Mean (SD)	NA	5, 0.17 (0.07)	5, 0.17 (0.10)	27, 0.41 (0.75)
	Median (Min, Max)	NA	0.13 (0.1, 0.2)	0.12 (0.1, 0.3)	0.19 (0.1, 4.0)
	On-demand				
	n, Mean (SD)	NA	-	-	13, 0.32 (0.15)
	Median (Min, Max)	NA	-	-	0.31 (0.1, 0.7)
	ITI	NA	-	-	-

Table 2 Incidence of Any Joint Operations During the Study by Age Group – SA Set

Treatment Arm[a]	Treatment Regimen[a]	Age Groups (Years) at Baseline 0-<2 (N=15)	2-<12 (N=74)	12-<18 (N=36)	≥18 (N=252)
ADVATE		N, n (%)	N, n (%)	N, n (%)	N, n (%)
	Prophylaxis	No Observations	70, 2 (2.9)	35, 1 (2.9)	204, 24 (11.8)
	On-demand		6, -	4, -	70, 5 (7.1)
	ITI		6, -	0, -	1, -

Table 3 Summary of Average Gilbert Score (All Joints) by Study Year and Last Observation during the Study - by Treatment Regimen and by Age Group – ADVATE - SA Set

	Age Group (years) 2-<12 (N=74)		12-<18 (N=36)		≥18 (N=252)	
	Treatment Regimen		Treatment Regimen		Treatment Regimen	
	Prophylaxis	On-Demand	Prophylaxis	On-Demand	Prophylaxis	On-Demand
Baseline						
n (missing)	19 (44)	3 (3)	15 (20)	0 (1)	99 (89)	29 (35)
Mean (SD)	0.3 (0.4)	0.4 (0.4)	0.2 (0.3)	-	2.4 (2.2)	2.3 (2.9)
Median	0.2	0.3	0.3	-	1.4	1.3
25Q - 75Q	0.0 - 0.5	0.0 - 0.8	0.0 - 0.4	-	0.7 - 4.0	0.4 - 2.7
5Q - 95Q	0.0 - 1.0	0.0 - 0.8	0.0 - 0.7	-	0.3 - 6.3	0.3 - 9.8
Min - Max	0.0 - 1.0	0.0 - 0.8	0.0 - 0.7	-	0.0 - 9.2	0.0 - 11.0
Visit=Year 1						
n (missing)	13 (60)	2 (1)	11 (21)	0 (2)	59 (130)	14 (45)
Mean (SD)	0.27 (0.40)	0.17 (0.24)	0.21 (0.21)	-	2.34 (1.87)	1.91 (2.24)
Median	0	0.17	0.33	.	1.8	1.33
25Q - 75Q	0.00 - 0.40	0.00 - 0.33	0.00 - 0.33	-	0.67 - 4.17	0.67 - 2.33
5Q - 95Q	0.00 - 1.33	0.00 - 0.33	0.00 - 0.50	-	0.33 - 5.83	0.33 - 9.00
Min - Max	0.0 - 1.3	0.0 - 0.3	0.0 - 0.5	-	0.2 - 6.3	0.3 - 9.0
Visit=Year 2						
n (missing)	8 (56)	1 (2)	7 (26)	1 (1)	62 (122)	17 (38)
Mean (SD)	0.27 (0.33)	0.00 (.)	0.43 (0.38)	0.50 (.)	2.23 (2.06)	1.29 (1.23)
Median	0.17	0.00	0.33	0.5	1.5	0.67
25Q - 75Q	0.00 - 0.50	0.00 - 0.00	0.00 - 0.83	0.50 - 0.50	0.67 - 3.67	0.50 - 1.50
5Q - 95Q	0.00 - 0.83	0.00 - 0.00	0.00 - 1.00	0.50 - 0.50	0.17 - 6.17	0.20 - 3.60
Min - Max	0.0 - 0.8	0.0 - 0.0	0.0 - 1.0	0.5 - 0.5	0.0 - 7.8	0.2 - 3.6
Visit=Year 3						
n (missing)	7 (53)	2 (1)	6 (24)	0 (2)	41 (136)	10 (40)
Mean (SD)	0.33 (0.46)	0.17 (0.24)	0.33 (0.42)	-	1.97 (1.94)	1.43 (1.11)
Median	0	0.17	0.17	.	1	0.92
25Q - 75Q	0.00 - 0.67	0.00 - 0.33	0.00 - 0.67	-	0.33 - 2.83	0.67 - 2.33
5Q - 95Q	0.00 - 1.17	0.00 - 0.33	0.00 - 1.00	-	0.33 - 5.50	0.33 - 3.50
Min - Max	0.0 - 1.2	0.0 - 0.3	0.0 - 1.0	-	0.0 - 7.0	0.3 - 3.5
Visit=Year 4						
n (missing)	4 (51)	0 (1)	5 (25)	2 (2)	29 (143)	6 (43)
Mean (SD)	0.29 (0.21)	-	0.51 (0.57)	0.00 (0.00)	1.53 (1.51)	0.78 (0.80)
Median	0.33	.	0.33	0	1.33	0.5
25Q - 75Q	0.17 - 0.42	-	0.33 - 0.40	0.00 - 0.00	0.33 - 2.00	0.33 - 0.83
5Q - 95Q	0.00 - 0.50	-	0.00 - 1.50	0.00 - 0.00	0.00 - 4.33	0.17 - 2.33
Min - Max	0.0 - 0.5	-	0.0 - 1.5	0.0 - 0.0	0.0 - 6.7	0.2 - 2.3
Visit=Year 5						
n (missing)	2 (40)	-	5 (26)	1 (2)	22 (129)	7 (38)
Mean (SD)	0.50 (0.24)	-	0.27 (0.19)	0.00 (.)	1.17 (1.15)	0.74 (0.66)
Median	0.5	-	0.33	0	0.58	0.5
25Q - 75Q	0.33 - 0.67	-	0.17 - 0.33	0.00 - 0.00	0.33 - 1.67	0.33 - 0.83
5Q - 95Q	0.33 - 0.67	-	0.00 - 0.50	0.00 - 0.00	0.00 - 3.33	0.33 - 2.17
Min - Max	0.3 - 0.7	-	0.0 - 0.5	0.0 - 0.0	0.0 - 3.7	0.3 - 2.2
Visit=Year 6						
n (missing)	2 (28)	-	6 (27)	1 (2)	17 (126)	2 (39)
Mean (SD)	0.00 (0.00)	-	0.44 (0.33)	0.00 (.)	0.84 (0.81)	1.17 (0.24)
Median	0	-	0.33	0	0.67	1.17
25Q - 75Q	0.00 - 0.00	-	0.33 - 0.83	0.00 - 0.00	0.33 - 1.00	1.00 - 1.33
5Q - 95Q	0.00 - 0.00	-	0.00 - 0.83	0.00 - 0.00	0.00 - 3.33	1.00 - 1.33
Min - Max	0.0 - 0.0	-	0.0 - 0.8	0.0 - 0.0	0.0 - 3.3	1.0 - 1.3
Visit=Year 7						
n (missing)	0 (21)	-	0 (29)	0 (2)	2 (121)	0 (38)
Mean (SD)	-	-	-	-	1.58 (1.77)	-
Median	.	-	.	.	1.58	.
25Q - 75Q	-	-	-	-	0.33 - 2.83	-
5Q - 95Q	-	-	-	-	0.33 - 2.83	-
Min - Max	-	-	-	-	0.3 - 2.8	-
Visit=Year 8						
n (missing)	0 (11)	-	0 (21)	0 (1)	1 (72)	2 (20)
Mean (SD)	-	-	-	-	1.67 (.)	1.08 (0.59)
Median	-	-	.	.	1.67	1.08
25Q - 75Q	-	-	-	-	1.67 - 1.67	0.67 - 1.50
5Q - 95Q	-	-	-	-	1.67 - 1.67	0.67 - 1.50
Min - Max	-	-	-	-	1.7 - 1.7	0.7 - 1.5
Visit=Last observation						
n (missing)	11 (0)	1 (0)	15 (0)	2 (0)	103 (0)	27 (0)
Mean (SD)	0.29 (0.37)	0.33 (.)	0.26 (0.28)	0.17 (0.24)	1.92 (1.89)	1.26 (1.71)
Median	0.33	0.33	0.33	0.17	1.17	0.83
25Q - 75Q	0.00 - 0.33	0.33 - 0.33	0.00 - 0.33	0.00 - 0.33	0.33 - 2.83	0.33 - 1.40
5Q - 95Q	0.00 - 1.17	0.33 - 0.33	0.00 - 0.83	0.00 - 0.33	0.17 - 6.00	0.33 - 2.67
Min - Max	0.0 - 1.2	0.3 - 0.3	0.0 - 0.8	0.0 - 0.3	0.0 - 7.3	0.2 - 9.0

Assessment of the Applicant's Response

As requested, the MAH provided additional separate analyses of joint health outcomes collected in the paediatric subset of the study population. As expected, paediatric subjects were characterized by a lower frequency of pre-existing target joints and low Gilbert scores at baseline. During the course of the study, paediatric subjects showed low frequencies of documented new arthropathies and rarely required joint operations. In addition, the Gilbert scores obtained in paediatric subjects remained low throughout the study, further supporting the conclusion of effective treatment.

Conclusion

Issue resolved.

Question 3

Some of the treatment-related (S)AEs reported in study 060902 (as summarized in source tables 14.04.05.t and 14.04.05.v) are currently not mentioned in section 4.8 of the ADVATE/ADYNOVI SmPCs. Consequently, the MAH's claim that there is no need to update the Product Informations requires further justification. The reported cases of treatment-related hepatitis C, epilepsy, jugular vein thrombosis and acute myocardial infarction are considered particularly noteworthy and should be further discussed on the basis of additional information.

Summary of the Applicant's Response

The reported cases of treatment-related hepatitis C, epilepsy, jugular vein thrombosis, and acute myocardial infarction are discussed below. None of these events are considered by the MAH to be related to ADVATE or ADYNOVI treatment.

Assessment of the Applicant's Response

As requested, the MAH provided additional information about the (S)AEs in question. Of note, two of these events (i.e. a case of Hepatitis C infection and a case of Jugular vein thrombosis) affected paediatric study subjects. However, in view of the newly provided information, the MAH's conclusion that these events were unlikely to be related to the administration of ADVATE or ADYNOVI is considered acceptable.

Conclusion

Issue resolved.

Question 4

The presentation of treatment-related (S)AEs reported in study 060902 covers the entire study population. To enable an assessment of safety in the paediatric subset, the MAH should provide separate presentations of treatment-related (S)AEs reported in study participant <18 years of age (i.e. <2 years, 2 to 12 years, 12-18 years) and critically discuss potential age-related differences.

Summary of the Applicant's Response

A separate analysis of (serious) adverse events ([S]AEs) reported in study participant aged <18 years at baseline (i.e. <2 years, 2 to 12 years, 12 to 18 years) has been added to the eCTD.

Non-interventional study - AHEAD 060902 - ADVATE / ADYNOVI Haemophilia A Outcome Database - EMA Analysis
Table 14.04.05.AGEG.t Treatment Related Adverse Events by MedDRA SOC and Preferred Term by Age Group
SA Set - ADVATE
Infants (age 0 to < 2 years)

System Organ Class Preferred Term	Prophylaxis (N=15)	On-demand (N=0)	ITI (N=2)	Total (N=15)
At least one treatment related AE	1 (6.7%) 1.2 1	- (-)	0 (0.0%) 0 0	1 (6.7%) 1.2 1
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (6.7%) 1.2 1	- (-)	0 (0.0%) 0 0	1 (6.7%) 1.2 1
FACTOR VIII INHIBITION	1 (6.7%) 1.2 1	- (-)	0 (0.0%) 0 0	1 (6.7%) 1.2 1

Children (age 2 to <12 years)

System Organ Class Preferred Term	Prophylaxis (N=70)	On-demand (N=6)	ITI (N=6)	Total (N=74)
At least one treatment related AE	3 (4.3%) 0.7 3	0 (0.0%) 0 0	1 (16.7%) 31.0 3	4 (5.4%) 1.2 6
INFECTIONS AND INFESTATIONS	1 (1.4%) 0.2 1	0 (0.0%) 0 0	1 (16.7%) 10.3 1	2 (2.7%) 0.4 2
DEVICE RELATED INFECTION	0 (0.0%) 0 0	0 (0.0%) 0 0	1 (16.7%) 10.3 1	1 (1.4%) 0.2 1
HEPATITIS C	1 (1.4%) 0.2 1	0 (0.0%) 0 0	0 (0.0%) 0 0	1 (1.4%) 0.2 1
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (1.4%) 0.2 1	0 (0.0%) 0 0	0 (0.0%) 0 0	1 (1.4%) 0.2 1
FACTOR VIII INHIBITION	1 (1.4%) 0.2 1	0 (0.0%) 0 0	0 (0.0%) 0 0	1 (1.4%) 0.2 1
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0 (0.0%) 0 0	0 (0.0%) 0 0	1 (16.7%) 10.3 1	1 (1.4%) 0.2 1
CONTUSION	0 (0.0%) 0 0	0 (0.0%) 0 0	1 (16.7%) 10.3 1	1 (1.4%) 0.2 1
PRODUCT ISSUES	0 (0.0%) 0 0	0 (0.0%) 0 0	1 (16.7%) 10.3 1	1 (1.4%) 0.2 1
DEVICE LEAKAGE	0 (0.0%) 0 0	0 (0.0%) 0 0	1 (16.7%) 10.3 1	1 (1.4%) 0.2 1
VASCULAR DISORDERS	1 (1.4%) 0.2 1	0 (0.0%) 0 0	0 (0.0%) 0 0	1 (1.4%) 0.2 1
JUGULAR VEIN THROMBOSIS	1 (1.4%) 0.2 1	0 (0.0%) 0 0	0 (0.0%) 0 0	1 (1.4%) 0.2 1

Adolescents (age 12 to < 18 years)

System Organ Class Preferred Term	Prophylaxis (N=35)	On-demand (N=4)	ITI (N=0)	Total (N=36)
At least one treatment related AE	2 (5.7%) 2.4 5	0 (0.0%) 0 0	- (-)	2 (5.6%) 2.3 5
GASTROINTESTINAL DISORDERS	1 (2.9%) 0.5 1	0 (0.0%) 0 0	- (-)	1 (2.8%) 0.5 1
TOOTH DISORDER	1 (2.9%) 0.5 1	0 (0.0%) 0 0	- (-)	1 (2.8%) 0.5 1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (2.9%) 0.5 1	0 (0.0%) 0 0	- (-)	1 (2.8%) 0.5 1
DRUG INEFFECTIVE	1 (2.9%) 0.5 1	0 (0.0%) 0 0	- (-)	1 (2.8%) 0.5 1
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (2.9%) 0.5 1	0 (0.0%) 0 0	- (-)	1 (2.8%) 0.5 1
PRODUCT PREPARATION ERROR	1 (2.9%) 0.5 1	0 (0.0%) 0 0	- (-)	1 (2.8%) 0.5 1

Non-interventional study - AHEAD 060902 - ADVATE / ADYNOVI Haemophilia A Outcome Database - EMA Analysis
Table 14.04.05.AGEG.v Treatment Related Adverse Events by MedDRA SOC and Preferred Term by Age Group
SA Set - ADYNOVI
Adolescents (age 12 to < 18 years)

System Organ Class Preferred Term	Prophylaxis (N=10)	On-demand (N=1)	ITI (N=0)	Total (N=11)
No data available				

Overall, the number of treatment-related (S)AEs was low across all paediatric subgroups. There were no critical differences worth noting, and type of events observed were unremarkable and expected, such as FVIII inhibition. The events of hepatitis C and jugular vein thrombosis were both assessed as unrelated by the MAH and are discussed in detail in response to Question 3.

Assessment of the Applicant's Response

As requested, the MAH provided additional separate analyses of treatment-related (S)AEs reported in the paediatric subset of the study population. In view of these newly provided analyses, and together with the additional information on selected AEs provided in response to Question 3, it is agreed with the MAH that the safety data obtained in study 060902 do not indicate critical/remarkable age-related differences.

Conclusion

Issue resolved.

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

The MAH provided satisfactory responses to the requests for additional information. In summary, the real-world data collected in study 060902 do not change the favourable benefit-risk profile of ADVATE and ADYNOVI in their approved indications. The newly presented data do not warrant any update of their Product information and no regulatory actions are required.

☒ **Fulfilled:**

No regulatory action required.