18 September 2025
EMADOC-1700519818-2630630
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Kovaltry

Octocog alfa

Procedure no: EMA/PAM/0000281517

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**
☐	CHMP Rapporteur AR	25 August 2025	22 August 2025
☐	CHMP comments	8 September 2025	8 September 2025
☐	Updated CHMP Rapporteur AR	11 September 2025	11 September 2025
☒	CHMP outcome	18 September 2025	18 September 2025

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1. Introduction

On 24 June 2025, the MAH submitted a completed paediatric study for Kovaltry, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

Assessor's comment:

The TAURUS study (PH-42199) was completed on 01 MAR 2021. According to Article 46, results from a study with paediatric data must be submitted within six months of study completion. However, since this study is not part of any post-authorisation measure or specific obligation, issue is not further pursued.

2. Scientific discussion

2.1. Information on the development program

2.1.1. Clinical study

PH-42199: A Multinational Phase IV Study Evaluating "Real World" Treatment Pattern in Previously Treated Hemophilia A Patients Receiving Kovaltry (Octocog alfa) for Routine Prophylaxis.

Assessor's comment:

Since this is a p46 procedure for a Phase 4 non-interventional study that is not part of the EU RMP, only the paediatric data are assessed.

Description

Study PH-42199 was a multinational, open-label, prospective, non-interventional, single arm observational study in PTPs of any age with haemophilia A receiving BAY 81-8973 as prophylaxis therapy.

MAH stated that the TAURUS study (protocol no. 18559) was a voluntary study for generation of real-world evidence data on prophylaxis with Kovaltry. It was a multinational, open-label, prospective, non-interventional, single arm observational study in PTPs of any age with haemophilia A receiving Kovaltry as prophylaxis therapy.

2.2. Information on the pharmaceutical formulation used in the study

Kovaltry (BAY 81-8973; octocog alfa) is a full-length recombinant human coagulation factor VIII (rFVIII) product, formulated with sucrose.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

TAURUS study, PH-42199, protocol no. 18559 which is entitled: "A multinational phase IV study evaluating "Real World" treatment pattern in previously treated hemophilia A patients receiving Kovaltry (octocog alfa) for routine prophylaxis."

The study was conducted at 25 study locations throughout Asia, Europe, and the USA.

All patients prescribed Kovaltry for a medically appropriate use, fulfilling the selection criteria and consenting to participate, were eligible for enrolment into the study. The recruitment period was 3.5 years and patients were followed up for a minimum of 1 year and up to approximately 2 years or until the end of treatment with BAY 81-8973.

Physicians collected historic data (demographic and clinical characteristics) from medical records, and treatment related data during visits that took place in routine clinical practice. Patients documented injections for prophylaxis, bleeding events and all other events that required FVIII injections in a patient diary. Validated patient questionnaires (Hemophilia Treatment Satisfaction Questionnaire [Hemo-SAT], Validated Hemophilia Regimen Treatment Adherence Scale [VERITAS-PRO]) were used as sources for the patient assessment on satisfaction and treatment adherence.

Due to the coronavirus disease (COVID-19) pandemic, the study was prematurely halted in all countries, except Italy, at the end of 2020. However, this decision had no impact on the safety or the physical or mental wellbeing of the study participants. The impact on the primary objective was considered minor since all patients could still be included in the analysis.

Methods

Study participants

Children and adults with moderate to severe haemophilia A (Factor VIII concentration [FVIII:C] (≤5%).

Male patients of any age treated with ≥50 EDs of any FVIII product; without history of inhibitors, or with previous history of inhibitors with at least 2 consecutive negative inhibitor tests and on standard prophylaxis therapy for at least 1 year prior to study entry; no other bleeding disorder.

A total of 320 patients were screened for this study. Of these, 318 patients (99.4%) enrolled.

Demographics and baseline characteristics

All 112 paediatric patients in the SAF were male, and most were white, not Hispanic or Latino. In the <6-year, ≥6 to <12-year and ≥12 to <18-year groups, the mean age for initiating prophylaxis therapy was 1.7, 2.7 and 3.8 years, respectively; and the median (range) length of continuous regular prophylaxis treatment prior to entry into this study was 1.3 (1.0–2.0), 6 (4.0-8.0) and 11.0 (9.0 – 13.0) years, respectively.

All paediatric patients in the SAF had prior FVIII treatment documented with majority (75.0%, 63.0% and 75.9% in the <6-year, ≥6 to <12-year and ≥12 to <18-year groups, respectively) treated with KOGENATE FS/Bayer. 8 patients < 18 years were receiving BAY 81-8973 as the current regimen prior to baseline (FAS- study medication- Table 14.1.1/5 in the MAH's documentation; not included in AR for the sake of conciseness). The dose frequency of most recent prophylaxis FVIII treatment regimen prior to BAY 81-8973 was >2.5x/week in 8 (66.7%), 28 (65.1%) and 35 (66.0%) patients in the <6-year, ≥6 to <12year and ≥12 to <18-year groups, respectively, and was ≤2.5x/week in 4 (33.3%), 15

(34.9%) and 18 (34.0%) patients in the <6-year, ≥6 to <12year and ≥12 to <18-year groups, respectively.

In total, 29 (25.9%) patients in the SAF had concomitant diseases at baseline.

Objective(s)

Table 1-1: Study objectives and variables

Objective	Variable
Primary objective	**Primary efficacy variable**
The primary objective of this study was to investigate weekly prophylaxis dosing regimens used in standard clinical practice.	Proportion of patients on 2x and 3x weekly prophylaxis at end of observation period
Secondary objectives	**Secondary efficacy variables**
To evaluate: • Effectiveness in prophylaxis • Prophylaxis dosing regimen in different age groups and countries • Consumption of KOVALTRY • Determinants for decisions on different prescribed regimens • Changes in treatment satisfaction (Hemo-SAT) after one year and two years of treatment (in countries where validated and applicable) • Changes in treatment adherence (VERITAS-PRO) after six months, one year and two years of treatment (in countries where validated and applicable) • Evaluation of safety in patients treated with KOVALTRY for up to two years • Describe approach to PK dosing and collection of KOVALTRY PK data if performed	• Annualized number of reported bleeds (total, spontaneous, joint and trauma) • Prophylaxis dosing by age group and country • Change in prophylaxis dosing frequency and reason for change (study start to end of observation period) • The total annualized factor consumption • Physician decision determinants of prophylaxis regimen • Change from baseline to one year and two years in treatment satisfaction (Hemo-SAT) • Change from baseline to six months, one year and two years in treatment adherence VERITAS-PRO • Occurrence of AEs and SAEs • Frequency and type of data relating to KOVALTRY PK (e.g. FVIII trough, peak levels, half-life, in-vivo recovery and assay [one stage or chromogenic assay])

Study population

A total of 318 patients were enrolled in the study with the full analysis set (FAS) and safety analysis set (SAF) comprising 302 (95.0%), and 313 (98.4%) patients, respectively. Due to "no documented dose of Kovaltry", 5 patients were not included in the SAF. 110 PTPs in the FAS were children (11 aged <6 years and 46 aged ≥6 to <12 years) or adolescents (53 aged ≥12 to <18 years). 112 PTPs in the SAF were children (12 aged <6 years and 46 aged ≥6 to <12 years) or adolescents (54 aged ≥12 to <18 years).

For the <6-year, ≥6 to <12-year and ≥12 to <18-year groups the mean observation period for the final analysis was 466.8, 447.2 and 438.9 days, respectively for the SAF.

Demographics and baseline characteristics

All 112 paediatric patients in the SAF were male, and most were white, not Hispanic or Latino. In the <6-year, ≥6 to <12-year and ≥12 to <18-year groups, the mean age for initiating prophylaxis therapy was 1.7, 2.7 and 3.8 years, respectively; and the median (range) length of continuous regular prophylaxis treatment prior to entry into this study was 1.3 (1.0–2.0), 6 (4.0-8.0) and 11.0 (9.0 – 13.0) years, respectively.

All paediatric patients in the SAF had prior FVIII treatment documented with majority (75.0%, 63.0% and 75.9% in the <6-year, ≥6 to <12-year and ≥12 to <18-year groups, respectively) treated with Kogenate FS/Bayer. 8 patients < 18 years were receiving BAY 81-8973 as the current regimen prior to baseline. The dose frequency of most recent prophylaxis FVIII treatment regimen prior to BAY 81-8973 was >2.5x/week in 8 (66.7%), 28 (65.1%) and 35 (66.0%) patients in the <6-year, ≥6 to <12year and ≥12 to <18-year groups, respectively, and was ≤2.5x/week in 4 (33.3%), 15 (34.9%) and 18 (34.0%) patients in the <6-year, ≥6 to <12year and ≥12 to <18-year groups, respectively. In total, 29 (25.9%) patients in the SAF had concomitant diseases at baseline.

Assessor's comment:

Study PH-42199 (TAURUS) was a multinational, open-label, prospective, non-interventional, single arm observational study in PTPs of any age with haemophilia A receiving Kovaltry as prophylaxis therapy.

A total of 318 PTPs were enrolled in the study encompassing 302 (95.0%) patients in the FAS and 313 (98.4%) patients in the SAF. 110 PTPs in the FAS were children (11 aged <6 years and 46 aged ≥6 to <12 years) or adolescents (53 aged ≥12 to <18 years). 112 PTPs in the SAF were children (12 aged <6 years and 46 aged ≥6 to <12 years) or adolescents (54 aged ≥12 to <18 years).

Biopharmaceutics/pharmacology

No additional information relevant to the biopharmaceutics or pharmacology of BAY 81-8973 is provided in this submission. Considering that TAURUS is an observational study, the registry of PK parameters was optional and aligned with routine clinical practice; therefore, reported PK data were limited. Less than half of the patients included in this analysis had their PK assessments carried out since the start of their treatment with BAY 81-8973, and one-stage assay-based PK assessments were performed more frequently than chromogenic assay-based assessments.

Results

Efficacy results

The results for the primary endpoint (proportion of patients on 2x and 3x weekly prophylaxis at end of observation period) in the subgroup analysis by age category (<12 years: N=57 and ≥12 years: N=245) were in line with results for the overall population: patients were treated most frequently 3 times per week, followed by 2 times per week and every other day at baseline and at end of observation.

Data on weekly dose of most recent FVIII treatment prior to BAY 81-8973 and for BAY 81-8973 at end of observation by different age categories (<6 years, ≥6 to <12 years, and ≥12 to <18 years) are presented in Table 4-1.

As in the overall population, a clear majority of patients in the <12 years (45 [78.9%]) and ≥12 years (210 [85.7%]) subgroups had no switch of prophylaxis dosing regimen from baseline to end of observation. 8 (14.0%) patients <12 years old and 18 (7.3%) patients ≥12 years old had an increase of prophylaxis dosing regimen. Very similar proportion of patients in these subgroups had a decrease

of prophylaxis dosing regimen from baseline to end of observation (4 [7.0%] and 17 [6.9%], respectively).

Table 4-1: Weekly dose of most recent FVIII treatment prior to KOVALTRY and of KOVALTRY at end of observation by age group (FAS)

	Prior to KOVALTRY Total weekly dose of most recent FVIII treatment prior to KOVALTRY, IU/kg			End of Observation Weekly prescribed dose at end of observation, IU/kg		
	<6 years N=11	≥6 to <12 years N=46	≥12 to <18 years N=53	<6 years N=11	≥6 to <12 years N=46	≥12 to <18 years N=53
n	11	42	51	11	45	52
Nmiss	0	4	2	0	1	1
Mean (SD)	108.152 (82.582)	80.761 (50.584)	62.992 (46.273)	100.619 (76.986)	88.010 (42.151)	77.495 (43.233)
Median	83.333	72.479	49.180	75.000	76.923	64.867
Min, Max	29.41, 315.79	30.00, 333.33	7.87, 249.11	29.41, 276.32	28.57, 195.12	20.16, 184.21

FAS: Full Analysis Set, Max: maximum, Min: minimum, n: number of patients, N: number of patients in subgroup or analysis set, Nmiss: number of patients with missing values in subgroup or analysis set, SD: standard deviation
Source: Module 5.3.5.2, PH-42199, Table 28

Assessor's comment:

The MAH states that the results from the primary endpoint (proportion of patients on 2x and 3x weekly prophylaxis at end of observation period) in the subgroup by age category (<12 years: N=57 and≥12 years: N=245) were in line with results for the overall population. Moreover, a majority of patients in the <12 years (45 [78.9%]) and ≥12 years (210 [85.7%]) subgroups had no switch of prophylaxis dosing regimen from baseline to end of observation. 8 (14.0%) patients <12 years old and 18 (7.3%) patients ≥12 years old had an increase of prophylaxis dosing regimen. Some patients in these subgroups had a decrease of prophylaxis dosing regimen from baseline to end of observation (4 [7.0%] and 17 [6.9%], respectively).

The Annualized Bleeding Rate (ABRs), treatment satisfaction, and adherence remained stable during the observation period:

- The median number of annualized reported total treated bleeds documented in patient diary was 2.0 (range: 0.00, 3.7), 1.6 (range: 0.00, 4.0) and 1.5 (range: 0.00, 3.5) for the total FAS in the <6-year, ≥6 to <12-year and ≥12 to <18-year groups. The median number of annualized reported total joint bleeds was 0.0 (range: 0.0 to 1.0), 0.0 (range: 0.0 to 2.3) and 1.0 (range: 0.00 to 2.0), respectively, and the median number of annualized reported spontaneous bleeds was 0.6 (range: 0.0 to 2.0), 0.0 (0.0; 2.3) and 0.9 (range: 0.0 to 1.4) in these groups, respectively. There were no differences in the median number of annualized reported trauma bleeds among the paediatric subgroups. The annualized number of reported bleeds stratified by dosing frequency and age group are shown in Table 4-2.

- Parents/caregivers for children (Hemo-SAT P) completed the Hemo-SAT questionnaire at the start and end of study. The treatment satisfaction level (Hemo- SAT P) among patients in the FAS at one and two years after initial visit did not change drastically. The median total Hemo-SAT P scores were 10.7 and 9.6 at 1 and 2 years from baseline, respectively.

The treatment adherence level among patients in the FAS at half year, one year and two years after initial visit remained relatively stable and no major differences were observed between the subgroups by baseline prophylaxis dosing regimen. However, results should be interpreted with caution due to few documented Hemo-SAT P questionnaires at the later time points in both the prophylaxis dosing regimen groups.

Table 4-2: Annualized bleeding rates of patients receiving KOVALTRY regular prophylaxis in the ≤2.5x/week and >2.5x/week KOVALTRY regimen groups at baseline stratified by age group.

Age category	Dosing frequency (times per week)	Number of patients (n)	ABR, median (Q1; Q3)			
			Total ABR	Joint ABR	Spontaneous ABR	Trauma ABR
<6 years	>2.5	8	0.3 (0.0; 2.7)	0.0 (0.0; 0.8)	0.0 (0.0; 1.7)	0.0 (0.0; 0.0)
	≤2.5	3	5.1 (2.0; 11.1)	0.0 (1.0; 4.1)	1.0 (0.9; 2.0)	3.4 (1.0; 9.1)
	Total	**11**	**2.0 (0.0; 3.7)**	**0.0 (0.0; 1.0)**	**0.6 (0.0; 2.0)**	**0.0 (0.0; 1.0)**
≥6 to <12 years	>2.5	26	0.9 (0.0; 3.5)	0.0 (0.0; 1.1)	0.0 (0.0; 2.0)	0.0 (0.0; 1.6)
	≤2.5	17	3.0 (0.0; 5.5)	1.0 (0.0; 3.5)	0.0 (0.0; 3.0)	0.0 (0.0; 1.7)
	Total	**43**[a]	**1.6 (0.0; 4.0)**	**0.0 (0.0; 2.3)**	**0.0 (0.0; 2.3)**	**0.0 (0.0; 1.7)**
≥12 to <18 years	>2.5	29	1.7 (0.5; 6.5)	1.0 (0.0; 3.1)	0.9 (0.0; 2.0)	0.5 (0.0; 2.0)
	≤2.5	16	1.0 (0.0; 2.4)	0.8 (0.0; 1.7)	0.5 (0.0; 1.3)	0.0 (0.0; 0.5)
	Total	**45**[a]	**1.5 (0.0; 3.5)**	**1.0 (0.0; 2.0)**	**0.9 (0.0; 1.4)**	**0.0 (0.0; 1.4)**

a Number of patients with missing data: ≥6 to <12 years, n = 3; ≥12 to <18 years, n = 8;.
Source: Module 5.3.5.2, PH-42199, FAS-Table 14.1.7/7

Of the patients <18 years with information on surgeries, 19 patients had one surgery, 3 patients had 2 surgeries, and 3 patients had 3 surgeries. A total of 7 patients had a major surgery and the majority of patients had minor surgeries (one minor surgery in 12 patients, and 2 and 3 minor surgeries in 3 patients each). Of the 34 surgeries documented during the study in patients <18 years of age, 28 surgeries were elective and 6 surgeries were emergency. No complications were reported and FVIII infusions were received during 32 surgeries.

For patients <12 years old, the median total annualized factor consumption for prophylaxis, bleeds and other events was 5535.391 IU/kg/year (range: 2978.23 to 16866.06) for patients <6 years old (n=11) and 3953.473 IU/kg/year (range: 2141.14 to 13527.01) for patients ≥6 to <12 years old (n=43); and was 3777.307 IU/kg/year (range: 0.00 to 11910.33) for patients ≥12 years old (n=212).

Assessor's comment:

The median ABR was 2.0 in the <6-year group, 1.6 in ≥6 to <12-year and 1.5 in the ≥12 to <18-year group. For joint bleeds, the median number of annualized reported was 0.0 in the <6-year group, 0.0 in the ≥6 to <12-year group and 1.0 in the ≥12 to <18-year group. The median number of annualized reported spontaneous bleeds was 0.6 for the <6-year group, 0.0 in the ≥6 to <12-year group and 0.9 in the ≥12 to <18-year group.

There were no differences in the median number of annualized reported trauma bleeds among the paediatric subgroups.

In the study supporting marketing authorisation in the paediatric population, the median ABR was 2.0 in the <6-year group and 0.9 in ≥6 to <12-year group. The ABR in ≥6 to <12-year group the was thus somewhat higher in the TAURUS study. This is noted but not further pursued since the difference between the studies are relatively small.

Safety results

Exposure

The median (Q1; Q3) weekly doses for BAY 81-8973 prophylaxis during the study in the <6- year, ≥6 to <12-year and ≥12 to <18-year groups in the FAS at baseline were 75.0 (29.4; 276.3), 76.9 (28.6;195.1) and 64.9 (20.2; 184.2) IU/kg, respectively. When stratified by age, median (range) of prescribed BAY 81-8973 doses for patients <12 years old (n = 54) and ≥12 years old (n = 228) were 75.58 (29.41– 276.32) IU/kg and 66.67 (11.90–228.26) IU/kg, respectively.

Adverse events

Overall frequency of adverse events

Of the 112 patients <18 years in SAF, 37 patients (33.0%) experienced at least one AE. All reported AEs were TEAEs. Patient-based incidences for TEAEs by age category were: 6 of 12 (50.0%) patients in the <6-year group, 17 of 46 (37.0%) patients in the ≥6 to <12-year group, and 14 of 54 (25.9%) patients in the ≥12 to <18- year group (Table 5-1).

Table 5-1: Overview of TEAEs (SAF) stratified by age group

	<6 years N=12 (100%)	≥6 to <12 years N=46 (100%)	≥12 to <18 years N=54 (100%)
Number of patients with any TEAE	6 (50.0%)	17 (37.0%)	14 (25.9%)
Number of patients with serious TEAE	3 (25.0%)	9 (19.6%)	3 (5.6%)
Number of patients with drug-related TEAE	0	0	0
Number of patients with serious drug-related TEAE	0	0	0
Number of patients with fatal TEAE	0	0	0
Number of patients with TEAE leading to discontinuation of KOVALTRY treatment	0	0	0
Number of patients with TEAE related to inhibitor development	0	0	0

Source: Module 5.3.5.2, PH-42199, SAF-Table 14.1.7/1

Overall, the highest incidence of TEAEs in patients <18 years was seen in the following MedDRA SOCs:

- Injury, poisoning and procedural complications in 18 (16.1%) paediatric patients with the most frequent PTs being 'fall' (n=5), 'injury' (n=4), and 'ligament sprain' (n=2)
- Musculoskeletal and connective tissue disorders in 14 (12.5%) paediatric patients with the most frequent PTs being 'arthralgia' (n=7), 'haemarthrosis' (n=4), and 'pain in extremity' (n=2).
- Infections and infestations (n=5, 4.5%).

  General disorders and administration site conditions (n=5, 4.5%) For SOCs and PTs occurring in >1 paediatric patient see Table 5-2.

Table 5-2: Patient based incidences of TEAEs (cut-off >1% of total patients) by SOC and PT (SAF) stratified by age group

MedDRA primary SOC PT	<6 years N=12 (100%)	≥6 to <12 years N=46 (100%)	≥12 to <18 years N=54 (100%)
Number (%) of patients with at least one such adverse event	6 (50.0%)	17 (37.0%)	14 (25.9%)
Gastrointestinal disorders	0	4 (8.7%)	0
General disorders and administration site conditions	1 (8.3%)	1 (2.2%)	3 (5.6%)
Infections and infestations	3 (25.0%)	2 (4.3%)	0
Injury, poisoning and procedural complications	2 (16.7%)	11 (23.9%)	5 (9.3%)
Fall	1 (8.3%)	2 (4.3%)	2 (3.7%)
Injury	1 (8.3%)	3 (6.5%)	0
Ligament sprain	0	2 (4.3%)	0
Metabolism and nutrition disorders	0	0	1 (1.9%)
Musculoskeletal and connective tissue disorders	0	6 (13.0%)	8 (14.8%)
Arthralgia	0	2 (4.3%)	5 (9.3%)
Haemarthrosis	0	3 (6.5%)	1 (1.9%)
Pain in extremity	0	1 (2.2%)	1 (1.9%)
Nervous system disorders	0	2 (4.3%)	1 (1.9%)
Skin and subcutaneous tissue disorders	0	1 (2.2%)	1 (1.9%)

Treatment-emergent: Any event arising or worsening after start of KOVALTRY until 7 days after last intake.
Source: Module 5.3.5.2, PH-42199, SAF-Table 14.1.7/2

No study drug-related AEs, AEs leading to discontinuation of BAY 81-8973 treatment or AEs leading to death were reported in patients <18 years. No AEs related to the development of an inhibitor or positive inhibitor measurement were observed.

Deaths, serious adverse events and other significant adverse events

None of the patients <18 years of age died due to any AE. A total of 15 patients aged <18 years in SAF experienced SAEs. The most common SAEs at SOC level in patients <18 years were Musculoskeletal and connective tissue disorders in 4 patients, Infections and infestations in 3 patients, and Injury, poisoning and procedural complications and Congenital, familial and genetic disorders in 2 patients each. At PT level, haemarthrosis was most frequent with 4 patients, followed by vascular device infection in 2 patients.

Assessor's comment:

Out of the 112 patients under 18 years of age in the SAF population, 37 patients (33.0%) experienced at least one TEAEs. More specifically, 6 out of 12 patients (50.0%) in the <6-year group, 17 of 46 (37.0%) patients in the ≥6 to <12-year group, and 14 of 54 (25.9%) patients in the ≥12 to <18- year group experienced any TEAEs.

The most common TEAEs included injury, poisoning and procedural complications in 18 (16.1%), musculoskeletal and connective tissue disorders in 14 (12.5%) and infections and infestations (n=5, 4.5%).

A total of 15 patients experienced SAEs where the most common ones included musculoskeletal and connective tissue disorders in 4 patients, infections and infestations in 3 patients, and injury, poisoning and procedural complications and Congenital, familial and genetic disorders in 2 patients each.

In the original study LEOPOLD Kids, including subjects 0-12 years of age, the percentage of SAEs was 9.8% compared to approximately 20% in the same age span in TAURUS. The observational period in LEOPOLD Kids was however only six months.

None of the paediatric patients died or discontinued treatment due to TEAEs.

Development of inhibitors is a known risk in both plasma derived FVIII and recombinant FVIII. The occurrence of an antibody against factor VIII, a so-called inhibitor, is the most important complication in haemophilia treatment. Inhibitors occur very commonly in previously untreated patients (PUP) with severe haemophilia A, usually within the first 50 exposure days (ED) ("Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products" EMA/CHMP/BPWP/144533/2009 rev. 2). No patients developed FVIII inhibitors in Study PH-42199. Of note, the inclusion criteria for this study were patients with over 50 exposure days or without previous history of inhibitors with at least 2 consecutive negative inhibitor tests and on standard prophylaxis therapy for at least 1 year prior to study entry. All these factors contribute to a lower risk of inhibitor development for these patients.

In conclusion, the overall pattern of adverse events resembles the previously known pattern, hence there were no unexpected findings.

Discussion on clinical aspects

Study PH-42199 (TAURUS) was a multinational, open-label, prospective, non-interventional, single arm observational study in PTPs of any age with haemophilia A receiving Kovaltry as prophylaxis therapy.

The primary objective was to investigate weekly prophylaxis dosing regimens used in standard clinical practice. The primary efficacy variable was the proportion of patients on 2x and 3x weekly prophylaxis at end of observation period.

A total of 318 PTPs were enrolled in the study encompassing 302 (95.0%) patients in the FAS and 313 (98.4%) patients in the SAF. 110 PTPs in the FAS were children (11 aged <6 years and 46 aged ≥6 to <12 years) or adolescents (53 aged ≥12 to <18 years). 112 PTPs in the SAF were children (12 aged <6 years and 46 aged ≥6 to <12 years) or adolescents (54 aged ≥12 to <18 years).

The MAH states that the results from the primary endpoint (proportion of patients on 2x and 3x weekly prophylaxis at tend of observation period) in the subgroup by age category (<12 years: N=57 and≥12 years: N=245) were in line with results for the overall population. Moreover, a majority of patients in the <12 years (45 [78.9%]) and ≥12 years (210 [85.7%]) subgroups had no switch of prophylaxis dosing regimen from baseline to end of observation. 8 (14.0%) patients <12 years old and 18 (7.3%) patients ≥12 years old had an increase of prophylaxis dosing regimen. Some patients in these subgroups had a decrease of prophylaxis dosing regimen from baseline to end of observation (4 [7.0%] and 17 [6.9%], respectively).

The median ABR was 2.0 in the <6-year group, 1.6 in ≥6 to <12-year and 1.5 in the ≥12 to <18-year group. For joint bleeds, the median number of annualized reported was 0.0 in the <6-year group, 0.0 in the ≥6 to <12-year group and 1.0 in the ≥12 to <18-year group. The median number of annualized reported spontaneous bleeds was 0.6 for the <6-year group, 0.0 in the ≥6 to <12-year group and 0.9 in the ≥12 to <18-year group.

There were no differences in the median number of annualized reported trauma bleeds among the paediatric subgroups.

In the study supporting marketing authorisation in the paediatric population, the median ABR was 2.0 in the <6-year group and 0.9 in ≥6 to <12-year group. The ABR in ≥6 to <12-year group the was thus somewhat higher in the TAURUS study. This is noted but not further pursued since the difference between the studies are relatively small.

There were no differences in the median number of annualized reported trauma bleeds among the paediatric subgroups.

Out of the 112 patients under 18 years of age in the SAF population, 37 patients (33.0%) experienced at least one TEAEs. More specifically, 6 out of 12 patients (50.0%) in the <6-year group, 17 of 46 (37.0%) patients in the ≥6 to <12-year group, and 14 of 54 (25.9%) patients in the ≥12 to <18- year group experienced any TEAEs.

The most common TEAEs included injury, poisoning and procedural complications in 18 (16.1%), musculoskeletal and connective tissue disorders in 14 (12.5%) and infections and infestations (n=5, 4.5%).

A total of 15 patients experienced SAEs where the most common ones included musculoskeletal and connective tissue disorders in 4 patients, infections and infestations in 3 patients, and injury, poisoning and procedural complications and Congenital, familial and genetic disorders in 2 patients each.

In the original study LEOPOLD Kids, including subjects 0-12 years of age, the percentage of SAEs was 9.8% compared to approximately 20% in the same age span in TAURUS. The observational period in LEOPOLD Kids was however only six months.

None of the paediatric patients died or discontinued treatment due to TEAEs.

No patients developed FVIII inhibitors in study PH-42199. However, inhibitors are predominantly developed during the first 50 EDs of treatment in previously untreated patients. In this study, the inclusion criteria were patients with over 50 EDs and no history of previous inhibitors (2 consecutive negative inhibitor test) and hence the risk of inhibitor development would be lower for the patients in this study 3.

3. Rapporteur's overall conclusion and recommendation

In conclusion, there were no unexpected findings in terms of efficacy and safety and the variation is considered approvable.

The benefit-risk balance of Kovaltry remains positive.

☒ **Fulfilled:**

No regulatory action required.