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

Kovaltry

Octocog alfa

Procedure no: EMEA/H/C/003825/P46/009

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	16 Sept 2024	16 Sept 2024	☐
☐	CHMP Rapporteur Assessment Report	21 Oct 2024	17 Oct 2024	☐
☐	CHMP members comments	04 Nov 2024	N/A	☐
☐	Updated CHMP Rapporteur Assessment Report	07 Nov 2024	N/A	☐
☒	CHMP adoption of conclusions:	14 Nov 2024	14 Nov 2024	☐

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1. Introduction

On 29th of August 2024, the MAH submitted a completed paediatric study, PAC study (protocol no. 19855) conducted in a Chinese paediatric population, 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 PAC study was performed to fulfil post approval commitment received from the China National Medical Product Administration (NMPA) for additional efficacy and safety data in previously treated and previously untreated Chinese haemophilia A patients.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the PAC study (protocol no. 19855) was a post-approval commitment study in China. It is a multicenter, uncontrolled, open-label, single arm treatment, 2-part study in previously treated children and adolescents/adults with severe haemophilia A (Part A), and in previously untreated, and minimally treated (Part B) Chinese children with severe haemophilia A.

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:

PAC study, B003238, protocol no. 19855 which is entitled: "A Post Approval Commitment study to evaluate the efficacy, safety, and pharmacokinetics (PK) of Kovaltry in Chinese children, adolescents/adults with severe hemophilia A."

2.3.2. Clinical study

Study B003238: A Post Approval Commitment study to evaluate the efficacy, safety, and pharmacokinetics (PK) of Kovaltry in Chinese children, adolescents/adults with severe hemophilia A.

Description

Study B003238 (PAC study, protocol no. 19855) is a multicentre, uncontrolled, open-label, single arm treatment, 2-part study in previously treated children and adolescents/adults with severe haemophilia A (Part A), and in previously untreated, and minimally treated (Part B) Chinese children with severe haemophilia A.

The PAC study comprises the following study parts:

- Part A collected clinical data in 42 PTPs Chinese patients with severe haemophilia A (30 children [<12 years of age] and 12 adolescents/adults [≥12 years of age]) to provide additional efficacy and safety data for the use of BAY 81-8973 for prophylaxis and treatment of bleeding episodes in this patient population. The treatment duration was 6 months. All patients were evaluated for inhibitor development and incremental recovery. PK data were collected from 24 patients (12 children and 12 adolescents/adults).
- Part B assessed the efficacy and safety of BAY 81-8973 in 3 PUPs/MTPs Chinese children with severe haemophilia A. Study patients were to be treated until at least 50 EDs were achieved. All patients were evaluated for inhibitor development and incremental recovery.

Methods

Study participants

Part A (PTP): 44 patients were enrolled in Part A of the study. As 2 of these patients did not pass screening (1 screening failure and 1 due to parent/guardian's decision), 42 PTPs participated in Part A (30 in the <12 years age group and 12 in the ≥12 years age group). All 42 patients completed the 6-month treatment period with BAY 81-8973. The SAF and mITT are identical and include 30 treated patients <12 years and 12 treated patients ≥12 years age. No per protocol efficacy analysis was performed for Part A because only one patient <12 years (2.4%) was excluded from the PPS (i.e., the minimum of 5% of mITT specified in the study protocol was not reached).

Part B (PUPs/MTPs): 3 patients (2 Previously untreated and 1 minimally treated) were enrolled and treated in Part B of the study. One PUP prematurely discontinued the study due to his parent/guardian's withdrawal of consent on the same day the first study treatment was administered. The other 2 patients were each treated for at least 50 EDs with BAY 81-8973. The SAF and mITT are identical and include all 3 treated patients.

Treatments

All treatment decisions for identifying appropriate prophylactic treatment regimen were guided by clinical judgment based on the approved PI and the individual patient characteristics and treatment response.

Patients in **Part A** were treated for 6 months at the following doses according to the prescribing information (PI) for BAY 81-8973:

- Patients ≤12 years of age: 25 to 50 IU of BAY 81-8973 per kg body weight twice weekly, three times weekly, or every other day according to individual requirements for 6 months
- Patients >12 years: 20 to 40 IU of BAY 81-8973 per kg of body weight two or three times per week according to individual requirements for 6 months

Patients in **Part B** were to be treated until at least 50 ED were achieved.

- Prophylaxis treatment might begin with 15 to 50 IU/kg (minimum dose: 250 IU) at least 1 day a week; alternatively, prophylaxis could be started directly with a once-a- week schedule minimum dose of 250 IU for PUPs/MTPs of any weight.
- The starting dose could be tailored to the patient's weight or demonstrated bleeding tendency.
- Individual patient dose decisions were at the discretion of the investigator.

Patients received study drug for treatment at home.

BAY 81-8973 was also used for treatment of bleeding events and with surgical procedures. In case PUPs or MTPs would develop a factor VIII inhibitor, ITI treatment was to be provided at a dose of up to 200 IU/kg daily for up to a maximum of 18 months or until failure.

Objectives

Part A in PTPs (children <12 years of age and adolescents/adults ≥12 years of age)

The primary objective was to evaluate the efficacy of prophylaxis treatment with BAY 81-8973 in Chinese children (<12 years) and adolescents/adults (≥12 years) with severe haemophilia A. The primary effect variable was ABR of all bleeding episodes (sum of spontaneous bleeds and trauma bleeds excluding bleeding episodes due to surgery) during prophylaxis treatment.

The secondary efficacy variables were:

- ABR of bleeding episodes within 48h of previous prophylaxis infusion (total, joint, spontaneous, trauma) **(for Part A only)**
- ABR of total bleeding episodes during prophylaxis treatment **(for Part B only)**
- ABR of treated bleeding episodes (total, joint, spontaneous, trauma)
- ABR of target joint bleeding episodes
- Study patient's/caregiver's assessment of response to treatment of bleeding episodes (excellent, moderate, good, or poor)
- Physician's assessment of the response to treatment of bleeding episodes in minor surgery (excellent, moderate, good, or poor)
- Evaluate proportion of patients without bleeding episodes
- The number of infusions per bleeding episode
- Factor VIII usage (expressed as number of infusions and IU/kg per year, as well as IU/kg per event)
- Incremental recovery

Part B in PUPs/MTPs (children <6 years of age)

The primary objective was to assess the efficacy of BAY 81-8973 within 48 hours of previous prophylaxis infusion in previously untreated/minimally treated Chinese children (<6 years of age) with severe haemophilia A. The primary efficacy variable was ABR of all bleeding episodes (sum of spontaneous bleeds and trauma bleeds excluding bleeding episodes due to surgery) within 48 hours of a previous prophylaxis infusion.

The secondary efficacy variables were the same as in Part A.

Safety variables for both Part A and Part B included incidence of AEs and SAEs, FVIII inhibitor development as measured by Nijmegen-modified Bethesda assay: patients who developed positive inhibitor titers (Bethesda ≥0.6 BU/mL), safety laboratory variables and vital signs including systolic and diastolic blood pressure, heart rate and body temperature.

Other variables included PK evaluation for Part A only.

- Concentration-time courses of FVIII
- Evaluation of PK-parameters: Cmax, AUC, AUCnorm, AUC (0-t last), AUC (0-t last) norm, Cmax norm, clearance, MRT, Vss, and t½.

Study design

This is a multicentre, uncontrolled, open-label, single arm treatment, 2-part study in previously treated (Part A), previously untreated, and minimally treated (Part B) Chinese children and adolescents/adults with severe haemophilia A.

Study participants who developed high-titer inhibitor (>5 BU/mL, confirmed by central laboratory) related to study drug, that interfered with effective treatment with FVIII, might opt to enter optional immune tolerance induction (ITI) treatment with study drug or leave the study and be treated with other therapies outside of the study at the discretion of the investigator.

Part A (PTPs)

Part A was to assess the efficacy, safety, and PK of BAY 81-8973 in previously treated Chinese children and adolescents/adults with severe haemophilia A. Part A was planned to investigate a total of 42 PTPs.

PK was to be assessed in a subset of 12 children (<12 years) and 12 adolescents/adults (≥12 years).

Efficacy and safety data for use of BAY 81-8973 for treatment of bleeding episodes were also to be collected.

- Study participants were to be treated for 6 months at the following doses according to the prescribing information for BAY 81-8973:
    - Study participants ≤12 years of age: 25 to 50 IU of BAY 81-8973 per kg body weight twice weekly, three times weekly, or every other day according to individual requirements for 6 months.
    - Study participants >12 years: 20 to 40 IU of BAY 81-8973 per kg of body weight two or three times per week according to individual requirements for 6 months.
- Part A was to include 5 study visits (Screening, Baseline, Visit 3/Month 1, Visit 4/Month 2, Visit 5/Final visit/Early Termination). All participants were also to receive a safety follow-up call approximately 2 weeks after the final study visit.

Part A of the study was to collect clinical data in 42 previously treated Chinese participants with severe haemophilia A (30 children and 12 adolescents/adults) to provide additional efficacy and safety data for the use of BAY 81-8973 for prophylaxis and treatment of bleeding episodes in this patient population. Pharmacokinetic data were also to be collected from 24 participants.

Part B (PUPs/MTPs)

Part B was to assess the efficacy and safety of BAY 81-8973 in previously untreated/minimally treated Chinese children with severe haemophilia A. Part B was planned to investigate approximately 6 PUPs/MTPs.

Efficacy and safety data for the use of BAY 81-8973 for treatment of bleeding episodes were also to be collected.

- Study participants were to be treated until at least 50 ED was achieved.
    - Treatment may begin with start of prophylaxis with 15 to 50 IU/kg (minimum dose: 250 IU) at least 1 day a week; alternatively, prophylaxis could be started directly with a once-a-week schedule minimum dose of 250 IU for PUPs/MTPs of any weight.
    - The starting dose may be tailored to the participant's weight or demonstrated bleeding tendency.
    - Individual participant dose decisions were at the discretion of the investigator.
    - Part B was to include 8 study visits (Screening, Baseline, Visit 3 [approximately 5 ED], Visit 4 [approximately 10 ED], Visit 5 [approximately 15 ED], Visit 6 [approximately 20 ED], Visit 7/Interim visit [approximately 30 to 40 ED], and Visit 8/Final visit [50 ED]/Early Termination). All parents/caregivers of participants in Part B were also to receive a safety follow-up call approximately 2 weeks after the end of treatment.

Part B of this study was to collect clinical data to provide additional efficacy and safety data for the use of BAY 81-8973 for prophylaxis and treatment of bleeding episodes in this patient population.

Study population

Part A (PTPs)

44 patients were enrolled in Part A of the study. As 2 of these patients did not pass screening (1 screening failure and 1 due to parent/guardian's decision), 42 PTPs participated in Part A (30 in the <12 years age group and 12 in the ≥12 years age group). All 42 patients completed the 6-month treatment period with BAY 81-8973. The SAF and mITT are identical and include 30 treated patients <12 years and 12 treated patients ≥12 years age. No per protocol efficacy analysis was performed for Part A because only one patient <12 years (2.4%) was excluded from the PPS (i.e., the minimum of 5% of mITT specified in the study protocol was not reached).

The median age was 8.0 years (range 2.3 to 11.0) for the <12 years age group and 21.0 years (range 12.0 to 35.0) for the ≥12 years age group (including 5 patients aged 12 to <18 years). All patients were Chinese and were of Asian race.

36 (25 in the <12 years and 11 in the ≥12 years age group) of the 42 patients (85.7%) had severe haemophilia A (FVIII activity <1%) based on their historical records. 6 patients (5 in the <12 years and 1 in the ≥12 years age group) had historic FVIII level <2%, all were confirmed to have FVIII <1% at baseline.

Seven (23.3%) participants in the <12 years age group and 4 (33.3%) in the in the ≥12 years age group had a family history of haemophilia, but none had a family history of inhibitor.

In the <12 years age group, 2 (6.7%) received on demand treatment, 17 (56.7%) received regular prophylaxis treatment, and 11 (36.7%) received intermittent prophylaxis treatment with a FVIII product prior to the study. 21 (70%) participants had more than 20 EDs with any FVIII products during the previous 3 months.

The median number of any type of bleeds in the previous year was 8.0 (0 to 53) with median numbers of bleeds of 13.5, 4.0 and 9.0 corresponding to on-demand, regular prophylaxis and intermittent prophylaxis participants, respectively. The median number of joint bleeds in the previous year was 2.0 (0 to 18) and the percentage of participants with a history of target joints was 36.7%.

In the <12 years age group, 2 (16.7%) received on demand treatment, 5 (41.7%) received regular prophylaxis treatment, and 5 (41.7%)) received intermittent prophylaxis treatment with a FVIII product prior to the study. Ten (83.3%) participants had more than 20 EDs with any FVIII products during the previous 3 months.

The median number of any type of bleeds in the previous year was 9.5 (1 to 56) with median numbers of bleeds of 44.0, 4.0, and 9.0 corresponding to on-demand, regular prophylaxis and intermittent prophylaxis participants, respectively. The median number of joint bleeds in the previous year was 4.0 (0 to 54) and the percentage of participants with a history of target joints was 41.7%. The maximum number of 4 target joints was present in 1 (8.3%) participant in this age group.

Part B (PUPs/MTPs)

3 patients (2 PUPs and 1 MTP) were enrolled and treated in Part B of the study. One PUP prematurely discontinued the study due to his parent/guardian's withdrawal of consent on the same day the first study treatment was administered. The other 2 patients were each treated for at least 50 EDs with BAY 81-8973. The SAF and mITT are identical and include all 3 treated patients.

The median age was 25 months (range 13 to 33). All patients were Chinese and were of Asian Race.

All 3 patients had severe haemophilia A (FVIII activity <1%) based on their historical records. The MTP had received 1 previous ED before study enrolment.

Assessor's comment:

The study was a multicenter, uncontrolled, open-label, single arm treatment, 2-part study in previously treated (Part A), previously untreated, and minimally treated (Part B) Chinese children and adolescents/adults with severe haemophilia A.

In Part A, there were 30 children in < 12 years age group with a median age of 8.0 years and 12 adolescents in the above with a median age of 21.00 which included 5 patients aged 12-18 years of age. In Part B, the median age was 25 months (range 13 to 33 months).

Pharmacokinetics

Pharmacokinetic assessments were performed in Part A only. The study design involved plasma sampling for BAY 81-8973 quantification. A sparse sampling schedule was used for participants under 12 years (pre-infusion, 15 min, 4 h, and 24 h post-infusion), while a rich sampling schedule was applied to those aged 12 years and above (pre-infusion, 10 min, 30 min, 1 h, 4 h, 6 h, 24 h, and 30 h post-infusion). Samples were analysed using a validated Sponsor Specific Analytical Method Instruction validated at Q2 Solutions Laboratories China (QBEJ) for Factor VIII activity. Pharmacokinetic parameters for BAY 81-8973 were summarized using descriptive statistics.

Assessor's comment:

The sampling schedule is deemed adequate for assessing non-compartmental calculation of AUC. The plasma concentration values may be used in population PK and/or population PK/PD analyses which is not reported in the current assessment report.

Results

Pharmacokinetic results

Figure 1 presents a graphical summary of pharmacokinetic (PK) data for three age groups: <6 years, 6 to <12 years, and ≥12 years, displayed on a semilogarithmic scale.

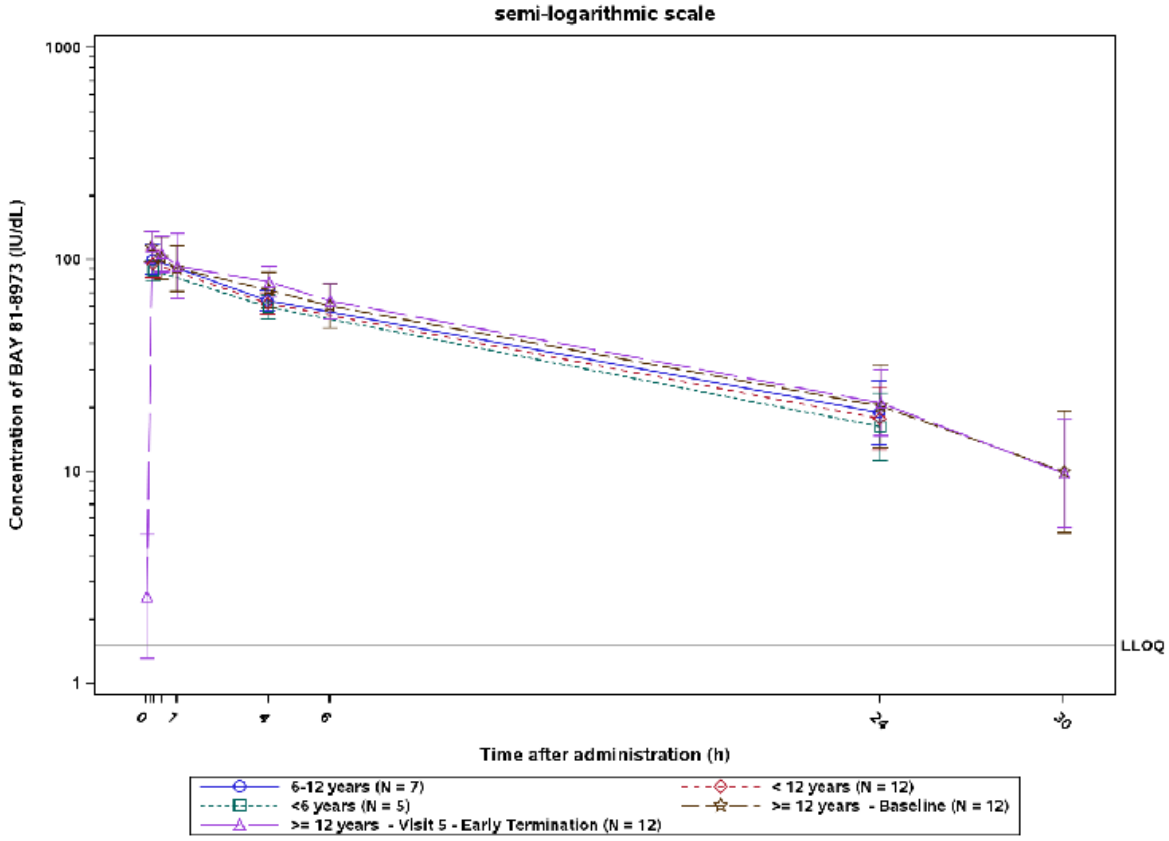

Figure 1 Geometric mean/SD for concentration of FVIII (IU/dL) in plasma (PK analysis set – Part A)

Table 1 provides a summary of the collected PK data at each sampling time point for each age group.

Table 1 Summary statistics for concentrations of FVIII (IU/dL) in plasma (PK analysis set – Part A)

Age Group	Visit	Time	n	n >= LLOQ	Geom. Mean (SD)	Geom. CV(%)	Arithm. Mean (SD)	Arithm. CV(%)	Median	Min, Max
<6 years	Baseline	PRE	5	1	N.C. (N.C.)	N.C.	N.C. (N.C.)	N.C.	N.C.	<LLOQ, 2.00
		0D 00H 15M	5	5	88.631 (1.12)	11.01	89.060 (9.811)	11.02	89.900	76.60, 103.20
		0D 04H 00M	5	5	59.553 (1.14)	12.82	59.940 (7.586)	12.66	58.500	50.30, 68.60
		1D 00H 00M	5	5	16.241 (1.44)	37.42	17.100 (6.025)	35.23	15.300	10.30, 23.80
6-12 years	Baseline	PRE	6	2	N.C. (N.C.)	N.C.	N.C. (N.C.)	N.C.	N.C.	<LLOQ, 2.80
		0D 00H 15M	7	7	100.186 (1.18)	16.46	101.286 (15.438)	15.24	104.800	73.60, 117.40
		0D 04H 00M	7	7	63.912 (1.12)	11.25	64.243 (6.763)	10.53	64.900	50.90, 72.10
		1D 00H 00M	7	7	18.873 (1.41)	35.47	19.886 (7.190)	36.16	18.000	11.80, 32.40
< 12 years	Baseline	PRE	11	3	N.C. (N.C.)	N.C.	N.C. (N.C.)	N.C.	N.C.	<LLOQ, 2.80
		0D 00H 15M	12	12	95.199 (1.16)	15.24	96.192 (14.305)	14.87	96.100	73.60, 117.40
		0D 04H 00M	12	12	62.058 (1.13)	11.92	62.450 (7.126)	11.41	64.850	50.30, 72.10
		1D 00H 00M	12	12	17.728 (1.41)	35.44	18.725 (6.592)	35.20	17.750	10.30, 32.40
>= 12 years	Baseline	PRE	12	2	N.C. (N.C.)	N.C.	N.C. (N.C.)	N.C.	N.C.	<LLOQ, 1.60
		0D 00H 10M	12	12	114.644 (1.17)	15.77	115.908 (17.544)	15.14	110.900	81.50, 141.20
		0D 00H 30M	12	12	101.812 (1.26)	23.26	104.200 (22.563)	21.65	105.400	69.00, 136.40
		0D 01H 00M	12	12	90.725 (1.28)	25.28	93.150 (21.066)	22.62	87.950	49.70, 129.00
		0D 04H 00M	12	12	71.629 (1.21)	19.40	72.900 (14.838)	20.35	68.450	57.20, 102.80
		0D 06H 00M	12	12	60.403 (1.27)	24.62	61.975 (14.116)	22.78	61.750	35.80, 85.30
		1D 00H 00M	12	12	20.272 (1.57)	47.55	22.133 (9.244)	41.77	24.650	9.60, 40.70
		1D 06H 00M	12	12	9.944 (1.94)	74.35	11.658 (5.532)	47.45	11.950	2.40, 18.20
	Final Visit/ Early Termination	PRE	12	11 s)	2.570 (1.97)	76.07	3.229 (2.666)	82.55	2.400	<LLOQ, 10.60
		0D 00H 10M	12	12	114.548 (1.19)	17.28	116.033 (18.623)	16.05	118.900	80.60, 137.40
		0D 00H 30M	12	12	106.088 (1.22)	19.74	107.900 (20.150)	18.67	106.300	72.80, 142.00
		0D 01H 00M	12	12	92.928 (1.43)	36.72	97.517 (26.987)	27.67	100.700	35.40, 135.40
		0D 04H 00M	12	12	78.504 (1.19)	17.27	79.583 (14.007)	17.60	81.050	62.00, 112.00
		0D 06H 00M	12	12	63.592 (1.21)	19.64	64.675 (12.138)	18.77	68.200	45.30, 87.90
		1D 00H 00M	12	12	21.022 (1.43)	36.87	22.225 (7.541)	33.93	22.450	11.20, 38.60
		1D 06H 00M	12	12	9.720 (1.80)	64.18	11.117 (5.181)	46.61	12.700	2.90, 17.60

N.C.: not calculated (less than 2/3 of values per timepoint are >= LLOQ)
s) Values below LLOQ were substituted by 1/2 LLOQ for the calculation of statistics (LLOQ = 1.5IU/dL)
Age group of <6 years and 6 to <12 years are the subgroup of <12 years
Bayer: /var/swan/root/bhc/818973/19855/stat/main03/prod/analysis/pgms/t_14_4_adpc_pk1.sas 22APR2024 10:07
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Non-compartmental AUC across the age groups are summarized in Table 2.

Table 2 Summary statistics of pharmacokinetic parameters of FVIII in plasma (non-compartmental) (PK analysis set – Part A)

Parameter (Unit)	Age Group	Visit	N/n	Geom. Mean (SD)	Geom. CV(%)	Arithm. Mean (SD)	Arithm. CV(%)	Median	Min, Max
AUC (h*IU/dL)	<6 years	Baseline	5/5	1200.62 (1.28)	24.99	1230.24 (304.71)	24.77	1134.24	931.0, 1576.2
	6-12 years	Baseline	7/7	1363.26 (1.24)	21.51	1391.19 (316.36)	22.74	1259.89	1107.8, 1943.3
	< 12 years	Baseline	12/12	1292.97 (1.25)	22.87	1324.12 (308.58)	23.30	1224.98	931.0, 1943.3
	>= 12 years	Baseline	12/12	1519.38 (1.37)	32.38	1589.34 (495.90)	31.20	1572.55	871.4, 2580.9
		Final Visit/ Early Termination	12/12	1559.29 (1.29)	26.16	1607.58 (423.58)	26.35	1581.67	1002.6, 2617.3
	Total	Baseline	24/24	1401.61 (1.32)	28.65	1456.73 (426.03)	29.25	1395.10	871.4, 2580.9
		Final Visit/ Early Termination	12/12	1559.29 (1.29)	26.16	1607.58 (423.58)	26.35	1581.67	1002.6, 2617.3
CMAX (IU/dL)	<6 years	Baseline	5/5	88.63 (1.12)	11.01	89.06 (9.81)	11.02	89.90	76.6, 103.2
	6-12 years	Baseline	7/7	100.19 (1.18)	16.46	101.29 (15.44)	15.24	104.80	73.6, 117.4
	< 12 years	Baseline	12/12	95.20 (1.16)	15.24	96.19 (14.30)	14.87	96.10	73.6, 117.4
	>= 12 years	Baseline	12/12	114.64 (1.17)	15.77	115.91 (17.54)	15.14	110.90	81.5, 141.2
		Final Visit/ Early Termination	12/12	115.95 (1.19)	17.47	117.48 (18.96)	16.14	118.90	80.6, 142.0
	Total	Baseline	24/24	104.47 (1.20)	17.96	106.05 (18.61)	17.55	105.30	73.6, 141.2
		Final Visit/ Early Termination	12/12	115.95 (1.19)	17.47	117.48 (18.96)	16.14	118.90	80.6, 142.0

Assessor's comment:

The PK appears comparable across age groups. However, from the summary statistics there appears to be an age-related effect on PK exposure (AUC and CMAX), where younger age correlates with lower PK exposure.

Efficacy results

Part A (PTPs)

The primary efficacy variable was annualized bleeding rate (ABR) of all bleeding episodes (sum of spontaneous bleeds and trauma bleeds exclude bleeding due to surgery) during prophylaxis treatment.

Results for the primary efficacy variable are summarized in Table 4-1 (numbered as in the applicant´s clinical overview). The median ABR under treatment with BAY 81-8973 scored below the previous 12 months bleed numbers: 2.00 bleeds per year vs 8.0 in the <12 years age group and 0.00 bleeds per year vs 9.5 in the ≥12 years age group (see table below).

Prophylaxis treatment with BAY 81-8973 was used in previously treated Chinese children and adolescents/adults with regards to the prevention of bleeds using prophylaxis dose regimens of 2 or 3 times per week or every other day with a mean dose per infusion administered in the <12 years age group and ≥12 years age group of 33.0 ± 5.3 IU/kg and 26.8 ± 3.9 IU/kg, respectively.

Table 4-1: Number of total bleeds and annualized number of bleeds (mITT - Part A)

	<12 years (N=30)	≥12 years (N=12)	Total (N=42)
At least 1 bleed?			
n	30 (100.0%)	12 (100.0%)	42 (100.0%)
NO	13 (43.3%)	7 (58.3%)	20 (47.6%)
YES	17 (56.7%)	5 (41.7%)	22 (52.4%)
Number of total bleeds			
n	30	12	42
Mean (SD)	1.70 (2.09)	0.92 (1.24)	1.48 (1.90)
Median	1.00	0.00	1.00
Q1, Q3	0.00, 3.00	0.00, 2.00	0.00, 3.00
Min, Max	0.0, 8.0	0.0, 3.0	0.0, 8.0
Sum	51.0	11.0	62.0
Number of total bleeds per year			
n	30	12	42
Mean (SD)	3.38 (4.17)	1.86 (2.54)	2.95 (3.81)
Median	2.00	0.00	1.96
Q1, Q3	0.00, 5.99	0.00, 4.03	0.00, 5.80
Min, Max	0.0, 16.3	0.0, 6.2	0.0, 16.3

Source: Module 5.3.5.2, B003238, Table 14.2/1

Applying this treatment regimen, 43.3% of the patients in the <12 years age group and 58.3% in the ≥12 years age group remained completely bleed free during the 6 months treatment period.

Part B (PUPs/MTPs)

For Part B, the primary efficacy variable was the ABR of all bleeding episodes within 48 hours of a previous prophylaxis infusion in previously treated or minimally treated haemophilia A Chinese children. None of the participants experienced bleeds within 48 h after a prophylaxis infusion. A total of 2 bleeds were reported throughout Part B, which were treated with BAY 81-8973 infusion.

Assessor's comment:

In Part A, a total of 62 bleeds were reported during prophylaxis treatment with a median ABR of 1.00 and 51 bleeds with a median ABR 2.00 in the <12 years age group and 11 bleeds were reported in the ≥12 years age group with a mean ABR of 0.00. In Part B, the ABR of all bleeding episodes within 48 hours was 0.00. However, in an EU article 46-procedur, the data should be presented in age groups of below and above 18 years of age and not < and > 12 years of age as presented in this report, in order to differentiate the paediatric data. Nevertheless, since the majority of the children were in the age group of <12 years of age and in addition there were few bleeds within the > 12 years of age group, the issue is not further pursued.

The results are consistent with previous data in children/adolescents/adults for BAY 81-8973 and is what is expected with successful prophylaxis.

Secondary and additional efficacy variables

ABR of bleeding episodes within 48h of previous prophylaxis infusion (total, joint, spontaneous, trauma) (for Part A only)

In participants <12 years of age, (n=30), a total of 34 bleeds were reported within 48h of the previous prophylaxis infusion, resulting in a mean and median ABR of 2.26 ± 3.10 and 0.00, respectively. The number of participants who experienced at least 1 bleed within 48h of the previous prophylaxis infusion was 14 (46.7%). 16 out of the 34 bleeds (47.1%[1]) were trauma bleeds and the remaining (18/34, 52.9%[1]) spontaneous bleeds, resulting in mean ABRs of 1.06 ± 1.70. Furthermore, 19 out of the 34 bleeds were joint bleeds (55.9%[1], mean ABR 1.26 ± 2.77, median 0.00).

In participants ≥12 years of age (n=12), a total of 8 bleeds were reported within 48 h of the previous prophylaxis infusion, resulting in a mean and median ABR of 1.36 ± 2.19 and 0.00, respectively. The number of participants who experienced at least 1 bleed within 48h of the previous prophylaxis infusion was 4 (33.3%). Half of the 8 bleeds were trauma bleeds and the other half spontaneous bleeds, resulting in mean ABRs of 0.68 ± 1.33 (median 0.00) and 0.68 ± 1.00 (median 0.00), respectively. Furthermore, 5 out of the 8 bleeds were joint bleeds (62.5%[1], mean ABR 0.84 ± 1.33, median 0.00).

ABR of total bleeding episodes during prophylaxis treatment (for Part B only)

A total of 2 bleeds were reported throughout Part B, 1 in each of the 2 participants who completed the study. Both bleeds were trauma bleeds and were treated with BAY 81-8973 infusions. Response to the treatment was assessed by the participant/caregiver as good for 1 bleed and moderate for the other.

ABR of treated bleeding episodes (total, joint, spontaneous, trauma)

In participants <12 years of age, 44 out of the 51 bleeds reported in this age group were treated bleeds (mean ABR 2.92 ± 4.19, median ABR 0.00), 21 (47.7%[1]) of which were trauma bleeds (mean ABR 1.39 ± 2.38, median ABR 0.00) and the remaining (23/44, 52.3%[1]) spontaneous bleeds (mean ABR 1.53 ± 3.65, median ABR 0.00). Furthermore, 31 out of the 44 treated bleeds were joint bleeds (70.5%[1], mean ABR 2.06 ± 4.09, median ABR 0.00).

In participants ≥12 years of age, 10 out of the 11 bleeds reported in this age group were treated bleeds (mean ABR 1.69 ± 2.28, median ABR 0.00), 4 (40.0%*) of which were trauma bleeds (mean ABR 0.68 ± 1.33, median ABR 0.00) and the remaining (6/10, 60.0%*) spontaneous bleeds (mean

[1] The percentage was manually calculated

ABR 1.02 ± 1.86, median ABR 0.00). Furthermore, 8 out of the 10 treated bleeds were joint bleeds (80%*, mean ABR 1.35 ± 2.00, median ABR 0.00).

ABR of target joint bleeding episodes

In participants <12 years of age, 2 out of the 7 participants with target joints confirmed at screening experienced a total of 9 joint bleeds, all of which affected target joints (mean ABR 2.52 ± 4.35, median ABR 0.00).

In participants ≥12 years of age, 2 out of the 5 participants with target joints confirmed at screening experienced a total of 4 joint bleeds, three of which affected target joints (mean ABR 1.22 ± 1.84, median ABR 0.00).

Study patient's/caregiver's assessment of response to treatment of bleeding episodes (excellent, moderate, good, or poor)

In participants <12 years of age, the response was assessed as "good" or "excellent" for 65.9% of the 44 treated bleeds. In only 1 (2.3%) of the treated bleeds was the response assessed as "poor".

In participants ≥12 years of age, the response was assessed as "good" or "excellent" for 70.0% of the 10 treated bleeds. None of the response was assessed as "poor".

Physician's assessment of the response to treatment of bleeding episodes in minor surgery (excellent, moderate, good, or poor)

In participants <12 years of age, the response was assessed as "good" or "excellent" for 65.9% of the 44 treated bleeds. In only 1 (2.3%) of the treated bleeds was the response assessed as "poor".

In participants ≥12 years of age, the response was assessed as "good" or "excellent" for 70.0% of the 10 treated bleeds. None of the response was assessed as "poor".

Evaluate proportion of patients without bleeding episodes

In participants <12 years of age, 43.3% did not experience any bleed and 66.7% did not experience any joint bleed during the prophylaxis treatment period. 53.3% of the participants did not experience any bleed within 48 hours of a previous prophylaxis infusion.

In participants ≥12 years of age, 58.3% did not experience any bleed or any joint bleed during the prophylaxis treatment period, and 66.7% did not experience any bleed within 48 hours of a previous prophylaxis infusion.

The number of infusions per bleeding episode

In participants <12 years of age, in total, 91 infusions of Kovaltry were administered for the treatment of 44 bleeds. The first infusion per bleed was given to treat a spontaneous bleed (23 bleeds [52.3%]), or to treat a trauma bleed (21 bleeds [47.7%]). The median number of infusions per bleed was 1.00 (range: 0.0 to 14.0). The majority of bleeds (84.3%) were successfully treated with ≤2 infusion, and 15.7% of the bleeds required ≥3 infusions. The median number of days between the previous prophylaxis treatment and a bleed was 1.31 days ranging from 0.1 to 9.5 days. The respective time was 1.00 day ranging from 0.1 to 3.4 days for spontaneous bleeds, and 1.86 days ranging from 0.1 to 9.5 days for trauma bleeds. For the 7 untreated bleeds, they resolved without any additional BAY 81-8973 infusion.

In participants ≥12 years of age, in total, 16 infusions of BAY 81-8973 were administered for the treatment of 10 bleeds. The first infusion per bleed was given to treat a spontaneous bleed (6 bleeds [60.0%]), or to treat a trauma bleed (4 bleeds [40.0%]). The median number of infusions per bleed was 1.00 (range: 0.0 to 4.0). The majority of bleeds (81.8%) were successfully treated with ≤2

infusion, and 18.2% of the bleeds required ≥3 infusions. The median number of days between the previous prophylaxis treatment and a bleed was 1.58 days ranging from 0.5 to 3.6 days. The respective time was 1.72 days ranging from 1.3 to 3.6 days for spontaneous bleeds, and 1.40 days ranging from 0.5 to 1.7 days for trauma bleeds. For the 1 untreated bleed, it resolved without any additional BAY 81-8973 infusion.

Factor VIII usage (expressed as number of infusions and IU/kg per year, as well as IU/kg per event)

In participants <12 years of age, the median BAY 81-8973 dose per infusion for bleeds was 31.22 IU/kg/infusion (range 26.3 to 37.1) and the median total dose per bleed was 1906.25 IU/bleed. The median total number of infusions required per subject for the treatment of bleeds during the study was 5.50 infusions and the median total annual dose used for the treatment was 297.56 IU/kg/year.

In participants ≥12 years of age, the median BAY 81-8973 dose per infusion for bleeds was 27.18 IU/kg/infusion (range 21.4 to 30.8) and the median total dose per bleed 1500.00 IU/bleed. The median total number of infusions required per subject for the treatment of bleeds during the study was 3.00 infusions and the median total annual dose used for the treatment was 132.66 IU/kg/year.

Incremental recovery

Incremental recovery of BAY 81-8973 showed mean in vivo recovery values of 1.82 ± 0.26 kg/dL for the <12 years age group and 2.03 ± 0.46 kg/dL for the ≥12 years age group at baseline. For both age groups, the recovery was stable over the 6 months treatment period.

Outcomes of surgeries

In participants<12 years of age two minor surgeries were performed (both dental extractions), with one mild bleed reported and treated with study drug after the surgery. There was no need for blood transfusions, and the haemostasis was assessed as excellent for both surgeries.

Participant ≥12 years of age, two minor surgeries were performed, which were 2 cases of gastroscopy 3 months apart for the same participant with no loss of bleed. There was no need for blood transfusions, and the haemostasis was assessed as excellent for both surgeries.

Assessor's comment:

In total, 62 bleeds were reported during the prophylaxis treatment; 51 bleeds (participants <12 years of age) and 11 bleeds (participants ≥12 years of age).

In participants <12 years of age, prophylaxis treatment with BAY 81-8973 was efficacious in previously treated Chinese children with regards to the prevention of bleeds using prophylaxis dose regimens of 2 or 3 times per week or every other day with a median dose of 31.6 IU/kg/infusion. In participants <12 years of age, 27 out of the 51 bleeds (52.9%) were trauma bleeds and the remaining 34 bleeds (47.1%) were spontaneous bleeds. 32 out of 51 bleeds were joint bleeds 62.7% and 28.13% of those were target joint bleeds. 34 bleeds were reported within 48h of the previous prophylaxis infusion. Most of the bleeds (84.3%) were successfully treated with ≤2 infusions of BAY 81-8973at doses between 26.3 and 37.1 IU/kg/infusion. Response to treatment was assessed as "good" or "excellent" for 65.9% of the treated bleeds.

In participants ≥12 years of age, prophylaxis treatment with BAY 81-8973 was efficacious in previously treated Chinese adolescents/adults with regards to the prevention of bleeds using prophylaxis dose regimens of 2 or 3 times per week with a median dose of 27.3 IU/kg/infusion. 4 out of the 11 bleeds 36.4% were trauma bleeds and the remaining 7 (63.6%) were spontaneous bleeds. 8 bleeds were reported within 48h of the previous prophylaxis infusion. Most of the bleeds (81.8%) were successfully treated with ≤2 infusions of BAY 81-8973 at doses between 21.4 and 30.8 IU/kg/infusion. Response to treatment was assessed as "good" or "excellent" for 70.0% of the treated bleeds.

In conclusion, the results are consistent with previous data from adults and children and what can be expected from prophylaxis treatment.

Safety results

All 42 treated participants, 30 in the <12 years age group and 12 in the ≥12 years age group, were included in the safety analysis.

Exposure

Part A

The mean time on study was 183.2 ± 3.7 days for patients <12 years of age and 181.2 ± 4.3 days for ≥12 years of age, during which the patients accumulated a median of 80.0 and 77.0 EDs to BAY 81-8973, respectively. Only 1 patient <12 years of age had less than 50 EDs (actual 45 EDs).

Part B (PUPs/MTPs)

For PUPs/MTPs, the mean time on study was 113.3 ± 97.7 days (median 161.0; range 1.0 to 178.0), during which 2 patients (1 PUP and 1 MTP) accumulated 51 EDs to BAY 81-8973 each. One PUP had less than 50 Eds.

Adverse events

Part A (PTPs)

TEAEs, i.e., AEs that started after the first BAY 81-8973 infusion and up to 3 days after the last dose, occurred in 16 (38.1%) patients (13 in the <12 years age group and 3 in the ≥12 years age group).

All TEAEs were mild or moderate in intensity, except for 1 severe TEAE occurring in the <12 years age group that was also serious (1 case of epilepsy).

Table 10-2: Summary of treatment-emergent adverse events in Part A (safety analysis set)

	< 12 years N=30 (100%)	>= 12 years N=12 (100%)	Total N=42 (100%)
Any AE	13 (43.3%)	3 (25.0%)	16 (38.1%)
Maximum intensity for any AE			
Mild	10 (33.3%)	3 (25.0%)	13 (31.0%)
Moderate	2 (6.7%)	0	2 (4.8%)
Severe	1 (3.3%)	0	1 (2.4%)
Any study drug-related AE	1 (3.3%)	0	1 (2.4%)
Maximum intensity for study drug-related AE			
Mild	1 (3.3%)	0	1 (2.4%)
Any AE related to procedures required by the protocol	0	0	0
Any SAE	2 (6.7%)	0	2 (4.8%)
Any SAE related to procedures required by the protocol	0	0	0
AE with outcome death	0	0	0

Source: Table 14.3.1 / 7

The highest incidence of TEAEs was seen in the following MedDRA system organ classes:

• Infections and infestations (n=10, 23.8%), with the most frequent preferred terms being 'upper respiratory tract infection' (n=6, 14.3%) or 'tonsillitis' (n=4, 9.5%).

• Gastrointestinal disorders (n=3, 7.1%), and

• Injury, poisoning and procedural complications in 2 (4.8%) patients. All other SOCs and preferred terms each affected 1 patient (see table below).

Table 10-3: Summary of treatment-emergent adverse events by primary system organ class and preferred term in Part A (safety analysis set)

Primary system organ class Preferred term MedDRA version 24.1	< 12 years N=30 (100%)	>= 12 years N=12 (100%)	Total N=42 (100%)
Number (%) of subjects with at least one such adverse event	13 (43.3%)	3 (25.0%)	16 (38.1%)
Gastrointestinal disorders	2 (6.7%)	1 (8.3%)	3 (7.1%)
Abdominal pain	1 (3.3%)	0	1 (2.4%)
Duodenal ulcer	0	1 (8.3%)	1 (2.4%)
Vomiting	1 (3.3%)	0	1 (2.4%)
General disorders and administration site conditions	1 (3.3%)	0	1 (2.4%)
Pyrexia	1 (3.3%)	0	1 (2.4%)
Infections and infestations	9 (30.0%)	1 (8.3%)	10 (23.8%)
Dermatitis infected	1 (3.3%)	0	1 (2.4%)
Gingivitis	1 (3.3%)	0	1 (2.4%)
Oral herpes	1 (3.3%)	0	1 (2.4%)
Tonsillitis	4 (13.3%)	0	4 (9.5%)
Upper respiratory tract infection	5 (16.7%)	1 (8.3%)	6 (14.3%)
Injury, poisoning and procedural complications	2 (6.7%)	0	2 (4.8%)
Animal bite	1 (3.3%)	0	1 (2.4%)
Ligament sprain	1 (3.3%)	0	1 (2.4%)
Musculoskeletal and connective tissue disorders	1 (3.3%)	0	1 (2.4%)
Haemarthrosis	1 (3.3%)	0	1 (2.4%)
Nervous system disorders	1 (3.3%)	0	1 (2.4%)
Epilepsy	1 (3.3%)	0	1 (2.4%)
Vascular disorders	0	1 (8.3%)	1 (2.4%)
Hypertension	0	1 (8.3%)	1 (2.4%)

Adverse events are sorted by alphabetical order of the MedDRA classification.
A subject is counted only once within each preferred term or any primary SOC.
Source: Table 14.3.1 / 9

One study drug-related TEAE (PT: vomiting) was reported in one patient in <12 years age group, which was mild in intensity.

Deaths, serious adverse events and other significant adverse events

Part A

No patient died or discontinued study treatment due to any AE. 2 treatment-emergent SAEs i.e., epilepsy and haemarthrosis were reported, occurring in a patient with medical history of epilepsy and a patient with a history of target joint, respectively. Neither of the SAEs was considered as study drug-related and the outcome for both was resolved (see table below).

Table 10-4: Listing of all SAEs during the study (safety population)

SID	Age (years)	Preferred term (MedDRA v. 24.1)	Reported term	Severity	Treatment emergent	Drug related	Outcome
540060005	8	Epilepsy	Epilepsy	Severe	Yes	No	Resolved
540150004	4	Haemarthrosis	Right ankle joint bleeding	Moderate	Yes	No	Resolved

Source: Listing 14.3.2/1

Part B (PUPs/MTPs)

TEAEs occurred in 2 (66.7%) patients (1 each in the PUP and MTP groups). All TEAEs were mild in intensity and were not study drug-related. By PT, the following TEAEs were reported in 1 patient each: diarrhoea, cough and rhinorrhoea in 1 PUP, and COVID-19 and respiratory tract infection in 1 MTP.

None of the TEAEs was considered serious or of special interest, and there were no TEAEs leading to discontinuation or death.

Assessor's comment:

TEAEs, i.e., AEs that started after the first infusion and up to 3 days after the last dose, occurred in 16 (38.1%) patients (13 in the <12 years age group and 3 in the ≥12 years age group). All TEAEs were mild except one case of epilepsy that was considered serious TEAE in Part A. The most common treatment-emergent adverse events (TEAE) were infections and infestations (n=10, 23.8%), gastrointestinal disorders (n=3, 7.1%), and Injury, poisoning and procedural complications in 2 (4.8%) patients. Two treatment-emergent SAEs were reported and included epilepsy and haemarthrosis and neither were considered treatment related. None of the patients died or discontinued treatment due to TEAEs.

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

FVIII inhibitors

No participant developed a positive FVIII inhibitor level (≥0.6 BU/mL; Nijmegen modified Bethesda assay) during the study, neither in PTPs nor in PUPs/MTPs. Note, 2 patients (1 PUP and 1 MTP) reached 51 EDs. In Part A, 1 patient (≥12 years) had family history of developing inhibitors. In Part B, none of the patients had a family history of developing inhibitors.

Assessor's comment:

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). Indeed, no patients developed FVIII inhibitors in study 19855. However, inhibitors are predominantly developed during the first 50 EDs of treatment in previously untreaded patients. In Part B of the study 19855, there were three patients, where only 2 had been previously untreated and 1 minimally treated patient. It is also noted that these PUPs/MTPs patients in Part B had no family history of developing inhibitors. With only three participants previously untreated or minimally treated, the safety data regarding development of inhibitors in Chinese children is limited. Ultimately, this does not affect the safety in the approved EU-population.

Clinical laboratory, immunogenicity and other safety evaluations

In general, none of the treatment-emergent shifts in safety laboratory evaluations were considered clinically meaningful. No TEAEs in the MedDRA primary SOC Investigations were reported.

Further safety analyses included the pre- and post-infusion values of systolic and diastolic blood pressure, heart rate, respiration rate and body temperature, and their changes from baseline. With the exception for an AE of hypertension (reported term: high blood pressure) reported in the ≥12 years age group, no relevant changes were detected for any of these parameters during the course of the study. The AE of hypertension was mild in intensity and was not assessed as study drug-related.

2.3.3. Discussion on clinical aspects

PAC study (protocol no. 19855) was a multicentre, uncontrolled, open-label, single arm treatment, 2-part study in previously treated children and adolescents/adults with severe haemophilia A (Part A), and in previously untreated, and minimally treated (Part B) Chinese children with severe haemophilia A.

The primary objective in Part A was to evaluate the efficacy of prophylaxis treatment with BAY 81-8973 in Chinese children (<12 years) and adolescents/adults (≥12 years) with severe haemophilia A. The primary objective in Part B was to assess the efficacy of BAY 81-8973 within 48 hours of previous prophylaxis infusion in previously untreated/minimally treated Chinese children (<6 years of age) with severe haemophilia A.

In Part A, the primary effect variable was ABR of all bleeding episodes (sum of spontaneous bleeds and trauma bleeds excluding bleeding episodes due to surgery) during prophylaxis treatment. The median ABR under treatment with BAY 81-8973 was 2.00 bleeds per year vs 8.0 in the <12 years age group and 0.00 bleeds per year vs 9.5 in the ≥12 years age group. However, in an EU article 46-procedur, the MAH should have presented the data in age groups of below and above 18 years of age and not < and > 12 years of age as presented in this report, in order to differentiate the paediatric data. Nevertheless, since the majority of the children were in the age group of <12 years of age and there were few bleeds in the >12 years of age group, the issue is not further pursued.

In Part B, the primary efficacy variable was ABR of all bleeding episodes (sum of spontaneous bleeds and trauma bleeds excluding bleeding episodes due to surgery) within 48 hours of a previous prophylaxis infusion. None of the participants experienced bleeds within 48 h after a prophylaxis infusion. A total of 2 bleeds were reported throughout Part B, which were treated with BAY 81-8973 infusion.

Of the reported 62 bleeds reported, 54 bleeds (44 in the <12 years and 10 in the ≥12 years age groups) were treated with the study drug. A majority of the bleeds were spontaneous bleeds (52.3% in <12 years and 60.0% in ≥12 years age groups) and the remaining (47.7% and 40.0%, respectively) were trauma bleeds. Furthermore, the majority of the treated bleeds in children (70.5%) and adolescents/adults (80.0%) were joint bleeds. In both age groups, all bleeds were of mild/moderate intensity except for one in adolescents. Most of the bleeds were successfully treated with ≤2 BAY 81-8973 infusions (84.3% in the <12 years age group and 81.8% in the ≥12 years age group). Response to treatment was assessed as good or excellent for most treated bleeds (66% in the <12 years age group and 70% in the ≥12 years age group).

TEAEs, i.e., AEs that started after the first infusion and up to 3 days after the last dose, occurred in 16 (38.1%) patients (13 in the <12 years age group and 3 in the ≥12 years age group). All TEAEs were mild except one case of epilepsy that was considered serious TEAE in the mITT population. The most common treatment-emergent adverse events (TEAE) were infections and infestations (n=10, 23.8%), gastrointestinal disorders (n=3, 7.1%), and Injury, poisoning and procedural complications in 2 (4.8%) patients. Two treatment-emergent SAEs were reported and included epilepsy and haemarthrosis and neither were considered treatment related. None of the patients died or discontinued treatment due to TEAEs. In conclusion, the overall pattern of adverse events resembles the previously known pattern, hence there were no unexpected findings.

No patients developed FVIII inhibitors in study 19855. However, inhibitors are predominantly developed during the first 50 EDs of treatment in previously untreaded patients. In Part B of the study 19855, there were three patients, where only 2 had been previously untreated and 1 minimally treated patient. It is also noted that these PUPs/MTPs patients in Part B had no family history of developing inhibitors. With only three participants previously untreated or minimally treated, the safety data regarding development of inhibitors in Chinese children is limited. Ultimately, this does not affect the safety in the approved EU-population.

In Part A, PK was evaluated. The sampling schedule is deemed adequate for assessing non-compartmental calculation of AUC. The plasma concentration values may be used in population PK and/or population PK/PD analyses which is not reported in the current assessment report. The PK appears overall comparable across age groups. However, from the summary statistics there appears to be an age-related effect on PK exposure (AUC and CMAX), where younger age correlates with lower PK exposure.

3. CHMP overall conclusion and recommendation

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

The benefit-risk balance of Kovaltry remains positive.

☒ Fulfilled:

No regulatory action required.