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Full Length Article

Continued benefit demonstrated with BAY 81-8973 prophylaxis in previously treated children with severe haemophilia A: Interim analysis from the LEOPOLD Kids extension study

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ABSTRACT

Introduction: BAY 81-8973 (Kovaltry®), a recombinant factor VIII (rFVIII) product, was efficacious and well tolerated in paediatric previously treated patients (PTPs) with severe haemophilia A for ≥50 exposure days (EDs) in the LEOPOLD Kids study. Because long-term prophylaxis (≥100 EDs) can provide substantial patient benefits, FVIII products should demonstrate long-term safety and efficacy.

Aim: To demonstrate long-term (≥100 EDs) efficacy and safety of BAY 81-8973 in paediatric PTPs.

Methods: PTPs aged ≤12 years with severe haemophilia A without inhibitors could continue in the ongoing open-label extension study after completing ≥50 EDs in the LEOPOLD Kids main study. Patients received BAY 81-8973 for prophylaxis (25–50 IU/kg ≥2×/week), bleed treatment, and surgery. Bleeds were documented in electronic patient diaries. Inhibitor development was monitored every 6 months.

Results: At the August 2017 interim data cutoff, 46 patients (median [range] age at enrolment, 6.0 [1.0–11.0] years) had spent a median (range) of 602.5 (148–1069) EDs and 4.6 (1.0–5.9) years in the main plus extension studies. Median (quartile [Q]1; Q3) annualised bleeding rate for bleeds within 48 h after a prophylaxis infusion and total bleeds was 1.0 (0.2; 1.9) and 2.0 (0.4; 3.6), respectively. Most (> 94%) bleeds were mild or moderate; 71.8% were treated with ≤1 infusion. BAY 81-8973 was also well tolerated with only one treatment-related adverse event (transient, low-titre inhibitor which did not require treatment adjustment).

Conclusion: BAY 81-8973 was efficacious for prophylaxis and treatment of bleeds during > 4.5 years in paediatric PTPs with severe haemophilia A.

1. Introduction

For patients with severe haemophilia A (factor VIII [FVIII]:C < 1%), routine prophylaxis with FVIII products to replace the missing clotting factor is the recommended standard of care [1,2]. Prophylaxis is highly effective to prevent bleeds, with particularly striking reductions in joint bleeds compared with on-demand treatment, thereby promoting the long-term preservation of joint and

Abbreviations: ABR, annualised bleeding rate; AE, adverse events; BU, Bethesda units; ED, exposure day; EHL, extended half life; PTP, previously treated patient; Q, quartile; rAHF-PFM, antihemophilic factor (recombinant) plasma/albumin-free method; rFVIII, recombinant factor VIII; rFVIII-FS, sucrose-formulated recombinant FVIII; SHL, standard half life

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musculoskeletal function [2–4]. To achieve optimal protection, experts recommend initiating prophylaxis as early as possible, before the occurrence of bleeds or shortly after the first joint or muscle bleed [1,5]. Even a small number of bleeds into a single joint can potentially cause irreversible damage, and beginning a regular prophylaxis regimen before age 3 or 4 years has been associated with improved long-term joint health [4,6,7], with prophylaxis considered standard of care for young patients [8]. Continuation of prophylaxis may then be beneficial throughout the patient's lifetime [2], and so it is critical that all products indicated for prophylaxis, and particularly those approved in children, can be demonstrated safe and effective over long-term use.

BAY 81-8973 (Kovaltry®; Bayer, Berkeley, CA, USA) is an unmodified, full-length recombinant human FVIII product that is approved for routine prophylaxis, treatment of bleeds, and perioperative management in adults and children with haemophilia A and has 8031 patient-years' experience to 31 August 2018. The recommended dose for prophylaxis is 20 to 40 IU/kg 2 or 3 times weekly in adolescents and adults, and 20 to 50 IU/kg twice weekly, 3 times weekly, or every other day in children aged ≤12 years [9,10]. BAY 81-8973 has an amino acid sequence identical to sucrose-formulated recombinant FVIII (rFVIII-FS; Kogenate FS®; Bayer), but is produced using enhanced manufacturing techniques that eliminate addition of human- and animal-derived raw materials yielding a FVIII product that has enhanced purity and improved glycosylation and sialylation compared with rFVIII-FS and antihemophilic factor (recombinant) plasma/albumin-free method (rAHF-PFM; Advate®; Shire; Westlake Village, CA, USA) [11,12]. Results from head-to-head clinical studies revealed that pharmacokinetic parameters of BAY 81-8973 were noninferior to those of rFVIII-FS [13] and were improved versus another rFVIII product, rAHF-PFM [14]. In addition, pharmacokinetic analyses were undertaken in previously treated patients (PTPs) aged < 12 years in the LEOPOLD programme. Although, as expected, differences in clearance were seen across age groups, the half-life of BAY 81-8973 was consistent across age groups [9,13,15].

To date, > 100 million IUs of BAY 81-8973 have been used in the LEOPOLD clinical programme. Safety and efficacy of BAY 81-8973 for prophylaxis, treatment of bleeds, and perioperative management has been demonstrated in several studies as part of the LEOPOLD clinical trial programme [16–19]. In LEOPOLD Kids, prophylaxis with BAY 81-8973 at least twice weekly was efficacious and well tolerated for ≥50 exposure days (EDs; approximately 6–8 months) in previously treated children aged ≤12 years [17]. Herein, we present interim results from the ongoing LEOPOLD Kids extension evaluating the long-term efficacy and safety of BAY 81-8973 in previously treated paediatric patients.

2. Methods

2.1. Patients

Patients who completed ≥50 EDs in part A of the LEOPOLD Kids main study, which enrolled previously treated children aged ≤12 years with severe haemophilia A without inhibitors, were eligible to continue in the extension for ≥100 EDs. Inclusion and exclusion criteria for the main study have been previously published [17]. Parents or legal representatives for each child provided written, informed consent and assent as appropriate, and the study was approved by each site's independent ethics committee or institutional review board. Study conduct was consistent with principles specified in the Declaration of Helsinki.

2.2. Study design

This open-label extension of the phase 3, uncontrolled LEOPOLD Kids study was conducted across 22 centres in 12 countries to evaluate the long-term efficacy and safety of BAY 81-8973 in the treatment of previously treated children with severe haemophilia A. Patients entered the extension study on a rolling basis as they completed the main study (i.e., had received ≥50 EDs), which was carried out from June 2011 until January 2013, and results of the ongoing extension are presented here up to a cutoff date of August 2017. In the main and extension studies, patients received 25 to 50 IU/kg BAY 81-8973 at least twice weekly, with regimen assignment and adjustments made according to investigator discretion. The full extension study report is expected to be available in September 2021.

2.3. Efficacy and safety assessments

The primary efficacy variable was annualised bleeding rate (ABR) for bleeds occurring within 48 h after a prophylaxis infusion, including spontaneous, trauma-related, and untreated bleeds, as well as infusions reported for an unspecified purpose. Additional efficacy variables included ABRs for total bleeds, joint bleeds, including bleeds into target joints (joints with ≥3 bleeds over a 6-month period), spontaneous bleeds, and trauma-related bleeds independent of time of last infusion, as well as severity of bleeds (mild, moderate, or severe), number of infusions required to treat bleeds and treatment efficacy rating by the patient or caregiver (excellent, good, moderate, or poor [Appendix 1]), via an electronic patient diary. The haemostatic efficacy of BAY 81-8973 during surgery was based primarily on each surgeon's assessment of haemostasis according to their experience with other factors. Bleeding events and treatment were documented by the patient or caregiver in electronic patient diaries, which were verified by the investigator.

Adverse events (AEs) including inhibitor development were monitored throughout the main study and extension. During the extension, inhibitor screening was performed every 6 months using the Nijmegen-modified Bethesda assay at a central laboratory; a positive inhibitor was defined as 2 measurements of ≥0.6 Bethesda units (BU) from 2 independent plasma samples.

2.4. Statistical analysis

Descriptive statistics (summary statistics for continuous variables and frequencies for categorical variables) were calculated. Efficacy and treatment exposure were summarised for the main study, extension, and both study phases combined for the total patient population as well as for subgroups based on patient age (aged < 6 years or aged 6–12 years). A responder analysis was performed, with response rate defined by ABR for joint bleeds (joint ABR ≤1; joint ABR > 1–≤4; joint ABR > 4).

3. Results

3.1. Patients

Of 51 patients who completed the LEOPOLD Kids main study, 46 patients aged 1 to 11 years (median age, 6 years at study inclusion) continued in the extension study, (parental consent was not given for the remaining 5 patients), for a total median (range) 4.6 (1.0–5.9) years of treatment. At the time of the interim analysis, 29 patients (63.0%) had completed the extension study, 16 patients (34.8%) were ongoing in the extension study, and 1 patient (2.2%) had discontinued due to a diagnosis of von Willebrand disease during the extension (previously misdiagnosed as severe haemophilia A). At entry into the main study, demographics were similar across patients aged < 6 years and patients aged 6 to 12 years, but disease characteristics varied (Table 1); specifically, fewer patients in the older group had received prophylaxis before enrolment in the main study, and more of these patients had target joints. Older patients also had a higher number of median bleeds prior to study entry.

Forty-two (91.3%) of the 46 patients in the extension study did not have their dosing frequency modified by their investigator; the majority of patients were treated 2 to 3 times per week (n = 16 [34.8%] and

Table 1
Demographics and baseline characteristics for patients in the extension study[a].

	Patients aged < 6 years (n = 22)	Patients aged 6–12 years (n = 24)	Total patients (N = 46)
Age, y			
Median (range)	4.0 (1.0–5.0)	9.0 (6.0–11.0)	6.0 (1.0–11.0)
Race, n (%)			
White	21 (95.5)	22 (91.7)	43 (93.5)
Black	1 (4.5)	2 (8.3)	3 (6.5)
BMI, kg/m^2			
Median (range)	15.0 (13.5–24.6)	16.7 (13.0–24.1)	15.7 (13.0–24.6)
Weight, kg			
Median (range)	18.3 (11.9–39.0)	30.9 (16.8–59.0)	23.5 (11.9–59.0)
Previous treatment, n (%)			
Prophylaxis	21 (95.5)	17 (70.8)	38 (82.6)
On demand	1 (4.5)	7 (29.2)	8 (17.4)
Patients with target joints, n (%)	5 (22.7)	9 (37.5)	14 (30.4)
Median (range) bleeds in the previous 12 months	2.0 (0–55.0)	5.0 (0–49.0)	4.5 (0–55.0)
Median (range) joint bleeds in the previous 12 months	0 (0–15.0)	1.5 (0–33.0)	0 (0–33.0)

BMI, body mass index.
[a] These values reflect baseline characteristics reported at the beginning of the main LEOPOLD Kids trial.

Table 2
Treatment exposure during LEOPOLD Kids.

	Extension study only			Main study plus extension		
	Patients aged < 6 years (n = 22)	Patients aged 6–12 years (n = 24)	Total patients (N = 46)	Patients aged < 6 years (n = 22)	Patients aged 6–12 years (n = 24)	Total patients (N = 46)
Days in study	1486 (175–1868)	1494 (200–1989)	1494 (175–1989)	1667 (357–1987)	1682 (370–2165)	1682 (357–2165)
Exposure days	493.5 (67–875)	576.0 (94–1011)	545.5 (67–1011)	561.0 (148–977)	635.0 (178–1069)	602.5 (148–1069)
Dose per infusion, IU/kg						
Total	37.7 (24.2–57.6)	31.1 (20.9–43.1)	33.6 (20.9–57.6)	37.8 (23.2–57.5)	31.0 (21.1–43.9)	34.3 (21.1–57.5)
For prophylaxis	37.7 (23.7–57.6)	30.9 (20.9–43.4)	33.5 (20.9–57.6)	37.8 (23.3–57.5)	31.1 (21.0–43.9)	34.2 (21.0–57.5)
To treat bleeds	37.0 (23.6–66.7)	33.7 (22.4–43.0)	35.1 (22.4–66.7)	36.2 (20.8–69.6)	33.0 (22.4–44.4)	34.7 (20.8–69.6)
Annual consumption, IU/kg						
Total	5351 (2610–7827)	4168 (2936–8049)	4758 (2610–8049)	5517 (2651–8356)	4228 (2896–8222)	4700 (2651–8356)
For prophylaxis	4984 (2536–7305)	4089 (2930–7829)	4646 (2536–7829)	5121 (2585–7521)	4127 (2891–7958)	4528 (2585–7958)
Number of infusions	512.0 (67–881)	583.5 (94–1019)	548.5 (67–1019)	580.5 (150–992)	643.0 (183–1077)	612.5 (150–1077)
Prophylaxis regimen, n (%)						
Every other day	2 (9.1)	5 (20.8)	7 (15.2)	2 (9.1)	5 (20.8)	7 (15.2)
3 times weekly	11 (50.0)	8 (33.3)	19 (41.3)	11 (50.0)	6 (25.0)	17 (37.0)
Twice weekly	8 (36.4)	8 (33.3)	16 (34.8)	8 (36.4)	8 (33.3)	16 (34.8)
Variable frequency	1 (4.5)	3 (12.5)	4 (8.7)	1 (4.5)	5 (20.8)	6 (13.0)

Values are expressed as median (range).

n = 19 [41.3%], respectively), with a smaller percentage being treated every other day (n = 7, 15.2%; Table 2). During the extension study, 1 patient, aged < 6 years, and 3 patients, aged 6 to 12 years, switched dosing frequency; 3 patients increased frequency (1 patient from 3 times weekly to every other day and 2 patients from twice weekly to 3 times weekly), and 1 patient switched twice (from every other day to 3 times weekly and then back to every other day).

3.2. Treatment exposure

At the time of the interim analysis, patients had accumulated a median (range) of 602.5 (148–1069) EDs over a period of 4.6 (1.0–5.9) years in the main and extension studies combined, which included 545.5 (67–1011) EDs and 4.1 (0.5–5.4) years in the extension only (Table 2). Patients received a median (range) of 612.5 (150–1077) infusions with a median (range) dose per infusion of 34.3 (21.1–57.5) IU/kg over the combined study phases. Duration in the studies was similar across younger and older patients, but older patients overall had more EDs and, adjusted for body weight, received slightly lower doses per infusion and had lower annual consumption compared with the younger cohort. These trends were consistent across the extension study only and the main plus extension studies combined.

3.3. Efficacy

ABRs for total and joint bleeds occurring within 48 h after a prophylaxis infusion were low for both age groups across the main and extension studies (Table 3). For the main and extension studies combined, median (quartile [Q]1; Q3) total ABRs within 48 h after a prophylaxis infusion were low, at 1.0 (0.3; 1.8) and 0.9 (0.1; 1.9) for patients aged < 6 years and 6 to 12 years, respectively.

Regarding total bleeds across age groups independent of time of last infusion, respective median (Q1; Q3) ABRs during the main study, extension study, and main plus extension studies combined were 1.9 (0.0;

Table 3
ABR (Q1; Q3) for bleeds occurring within 48 h of a prophylaxis infusion.

Median (Q1; Q3) and (mean [SD]) ABR	Patients aged < 6 years (n = 22)	Patients aged 6–12 years (n = 24)	Total patients (N = 46)
Total bleeds			
Main study	1.9 (0.0; 4.0) (2.2 [2.7])	0.0 (0.0; 2.0) (1.4 [2.8])	0.0 (0.0; 2.2) (1.8 [2.7])
Extension study	0.8 (0.0; 1.7) (1.7 [2.8])	1.0 (0.1; 1.6) (1.2 [1.3])	1.0 (0.0; 1.7) (1.4 [2.1])
Main study plus extension	1.0 (0.3; 1.8) (1.9 [2.8])	0.9 (0.1; 1.9) (1.2 [1.30])	1.0 (0.2; 1.9) (1.5 [2.1])
Joint bleeds			
Main study	0.0 (0.0; 0.0) (0.5 [1.1])	0.0 (0.0; 1.0) (0.9 [1.7])	0.0 (0.0; 0.0) (0.7 [1.5])
Extension study	0.3 (0.0; 0.9) (0.8 [1.6])	0.1 (0.0; 0.9) (0.6 [0.8])	0.2 (0.0; 0.9) (0.7 [1.2])
Main study plus extension	0.4 (0.0; 1.0) (0.8 [1.4])	0.2 (0.0; 1.2) (0.7 [0.8])	0.3 (0.0; 1.2) (0.7 [1.1])

ABR, annualised bleeding rate; Q1, quartile 1; Q3, quartile 3; SD, standard deviation.

6.0), 1.8 (0.3; 3.5), and 2.0 (0.4; 3.6) (Fig. 1), considerably lower compared with the median number of bleeds reported during the 12 months prior to study start (4.5 [0; 55]). Consistency in total ABRs across the main and extension studies resulted from a reduction in median bleeds for patients aged < 6 years and a corresponding increase in median bleeds for patients aged 6 to 12 years. Median ABRs for joint bleeds and spontaneous bleeds were < 1.0 for both age groups throughout both study phases, with slight increases in median ABRs for all patients for joint bleeds and spontaneous bleeds in the much longer extension study (Fig. 1). The median percentage of joint bleeds into target joints was 46.5% for the main and extension studies combined and 47.8% in the extension study alone. The percentage of joint bleeds into target joints was higher among younger patients compared with older patients (median for combined main and extension study, 75.0% vs 40.0%, respectively; median for extension, 66.7% vs 40.0%).

Patients experienced a total of 493 bleeds throughout the main and extension studies (patients aged < 6 years, n = 244 bleeds; patients aged 6–12 years, n = 249 bleeds), of which 405 occurred during long-term treatment in the extension study (median, 4.1 years). Thirty-two bleeds (6.5%) did not require treatment. For the remaining 461 bleeds, 57.0% of the infusions were for trauma-related bleeds, 39.3% were for spontaneous bleeds, 0.4% were for surgery, and 3.3% were categorised as other. The majority of all bleeds, (94.1%) were mild or moderate in severity, and 423/493 bleeds (85.8%) were treated with ≤2 infusions (median [range] dose per infusion to treat bleeds, 34.7 [20.8–69.6] IU/kg; Table 2). Response to treatment was rated by the patient or caregiver as good or excellent for 88.5% of treated bleeds.

The responder rate, defined by joint bleed ABR, for the main and extension studies is shown in Table 4. In the extension study, patients who had a joint ABR ≤1 were of similar age as those with joint ABR > 1 (median, 6.0 years for both groups) but were less likely to have target joints (10.0% vs 31.3% of patients had target joints) and had fewer joint bleeds in the previous 12 months (median, 0.0 vs 5.5).

3.4. Haemostasis during surgery

Four patients underwent one major surgery each during the LEOPOLD Kids extension. Before surgery the median overall ABR for these patients was 1.0 (mean, 2.7). Ratings of BAY 81-8973 haemostatic efficacy were available for two patients aged 7 and 10 years (who underwent an adenotonsillectomy and treatment for appendicitis, respectively) and were excellent in both instances. The weight-adjusted BAY 81-8973 doses on day of surgery for these four patients were 56.6, 59.2, 106.1, and 163.3 IU/kg.

Thirteen patients underwent a total of 18 minor surgeries (catheter-related surgery [n = 9], dental surgery [n = 4], gastroscopy, arthroscopy, nasal polyp removal, tymphanostomy tube replacement and biopsy [n = 1 for each]). Blood loss was only observed for major surgeries, except for one minor surgery (1 mL), and minimal in all cases (range: 0–50 mL) and haemostatic efficacy was rated as excellent for 14 (77.8%) and good for 4 (22.2%) of the minor surgeries.

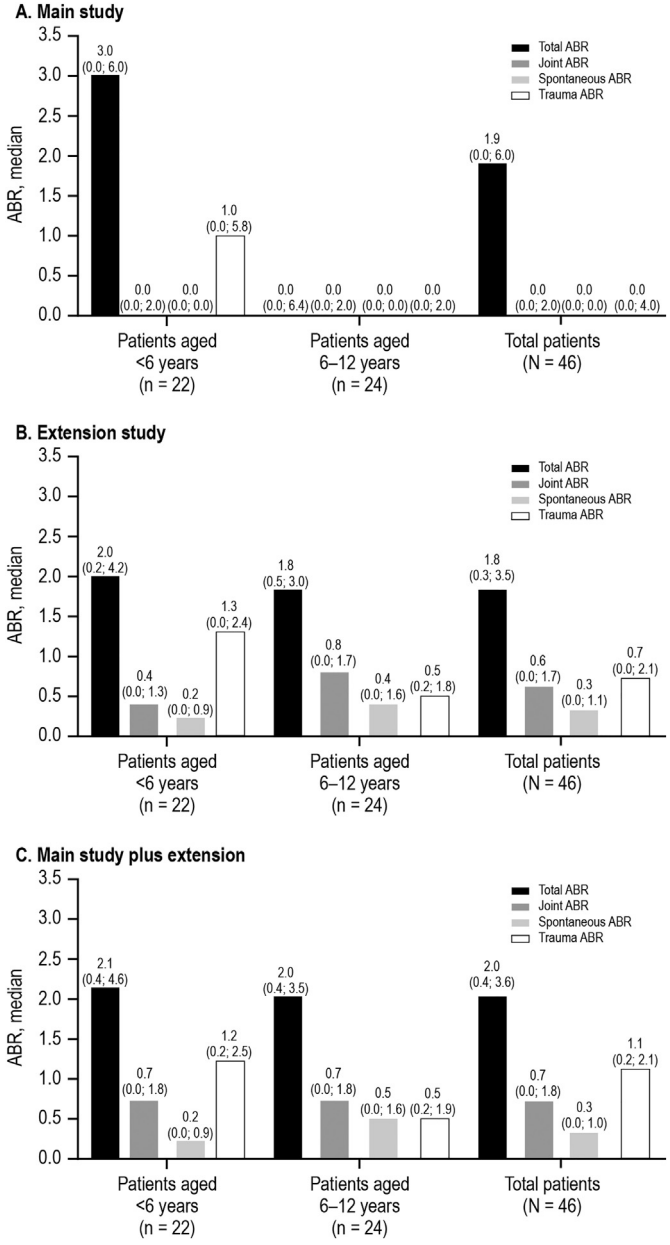

Fig. 1. Annualised bleeding rate (ABR) independent of time of last infusion during (A) the main study (≥50 EDs, over 6–8 months), (B) the extension (≥100 EDs, over approximately 4 years), and (C) the main study and extension combined. Data are median (quartile 1; quartile 3).

3.5. Safety

AEs were reported by all patients during the extension phase and were mostly mild (26.1%) or moderate (54.3%) in severity, and not related to study drug. The most frequent treatment-emergent AEs were tonsillitis (21.7%), cough (19.6%), headache (17.4%) and limb injury (15.2%). No patients discontinued the extension study following an AE. A single serious treatment-related AE was reported: mild, transient inhibitor development. This occurred in a patient aged 13 years who was

Table 4
Responder rate in the main study and extension.

	Patients aged < 6 years (n = 22)	Patients aged 6–12 years (n = 24)	Total patients (N = 46)
Main study, n (%)			
Joint ABR ≤1	15 (68.2)	17 (70.8)	32 (69.6)
Joint ABR > 1–≤4	6 (27.3)	4 (16.7)	10 (21.7)
Joint ABR > 4	1 (4.5)	3 (12.5)	4 (8.7)
Extension, n (%)			
Joint ABR ≤1	14 (63.6)	16 (66.7)	30 (65.2)
Joint ABR > 1–≤4	7 (31.8)	7 (29.2)	14 (30.4)
Joint ABR > 4	1 (4.5)	1 (4.2)	2 (4.3)

ABR, annualised bleeding rate.

previously treated with > 400 infusions of Immunate™ and Octanate® and had no history of inhibitors. The first positive inhibitor measurement at 549 EDs was 0.6 BU/mL and FVIII recovery was 2.2 IU/dL. The titre remained elevated at the next two measurements (572 EDs [0.8 BU/mL] and 626 EDs [1.0 BU/mL]), but was negative at the following study visit (703 EDs [< 0.2 BU/mL]). Titre in this patient remained ≤1.0 BU/mL and ultimately became negative with no changes in BAY 81-8973 dosing (at the time of analysis, the patient had four consecutive negative measurements and was continuing in the extension study).

4. Discussion

The LEOPOLD Kids extension study has provided long-term outcome data in children, indicating that BAY 81-8973 prophylaxis was efficacious and well tolerated for > 4.5 years in paediatric PTPs. Across the main (6–8 months) and extension (~4 years) studies, bleeding was assessed with a number of different parameters, the most important of which were bleeding within 48 h of infusion and overall bleeding rates. Median ABRs for total bleeds occurring within 48 h after a prophylaxis infusion and median ABRs for total bleeds were low and relatively consistent across both age groups and over the two study phases. Joint bleed ABR remained below 1.0 for all ages throughout the main and extension studies. ABRs for total bleeds observed with BAY 81-8973 in the LEOPOLD Kids main and extension studies were principally influenced by the number of trauma-related bleeds, with a low rate of spontaneous bleeds, and are comparable to published long-term paediatric efficacy data for other standard-half-life (SHL) and extended-half-life (EHL) rFVIII products when comparing several different dosing regimens [20–22]. The observed increase in ABR between the main study and extension study in patients aged 6–12 years may be a reflection of the higher level of activity in the older age group, but remains ≤2.0. Only very few patients required an adjustment in dosing frequency over the course of the extension period; alterations in dosing frequency may have been related to changes associated with the growth and activity of the children over time in this long-term extension.

The findings of this study are based upon an open-label extension of a previously reported single-arm clinical trial [17]. Nonetheless, our findings are consistent with previous reports of decreasing bleeding frequency with prolonged prophylaxis [4,23,24]. Bleeding events were collected via patient diaries without direct clinical confirmation; a method similar to other recent studies of FVIII products [4,24]. Similarly, haemostatic efficacy was self-reported using subjective scales, which demonstrated high patient satisfaction with the ability of BAY 81-8973 to adequately control bleeding episodes. Subjective evaluation of response is a well-established method in haemophilia A clinical research [25].

In the LEOPOLD Kids extension, BAY 81-8973 was also efficacious for the treatment of bleeds. Over 90% of bleeds were mild or moderate in severity, and 88.5% of treated bleeds were resolved with a good or excellent treatment efficacy rating. BAY 81-8973 was also useful for perioperative management: for all minor surgeries and the 2 major surgeries with available data regarding haemostatic efficacy of BAY 81-8973, perioperative management was rated as good or excellent.

Serious complications arise when a patient with haemophilia A develops an inhibitor, because inhibitors neutralise FVIII and make replacement treatment generally ineffective [2]. PTPs are considered to be the most appropriate population in which to evaluate immunogenicity of FVIII products [26]. Reassuringly, over a median duration of 4.1 years and 545.5 EDs in the LEOPOLD Kids extension study, only one patient developed a transient, low-titre (≤1.0 BU) inhibitor. There were no other study drug-related AEs during the extension study.

5. Conclusions

The LEOPOLD Kids extension has demonstrated excellent outcomes for paediatric patients using BAY 81-8973, which was efficacious and well tolerated to prevent and treat bleeds for > 4.5 years in previously treated children initially aged ≤12 years with severe haemophilia A. Patients maintained low ABRs with at least twice-weekly dosing, and most bleeds were controlled with ≤2 infusions. Long-term prophylaxis with BAY 81-8973 limits the number of bleeding episodes into joints, particularly among older children, which could preserve joint health, a critical outcome for promoting long-term joint function throughout the patient's lifetime. Importantly, there were no major safety concerns during long-term treatment with BAY 81-8973.

Author's contributions

G.K. contributed to data acquisition and interpretation, and critically reviewed all versions of the manuscript.
R.L. performed data analysis and interpretation.
L.R. performed the research and analysed the data.
B.K. contributed to data acquisition, analysis and interpretation.
V.B. reviewed all versions of the manuscript.
S.S. T. reviewed all versions of the manuscript.
V.U. reviewed all versions of the manuscript.
H.B. contributed towards data analysis and interpretation.
D.T-S. contributed towards data analysis and interpretation.
N.C. contributed towards data analysis and interpretation.
All authors critically reviewed the manuscript and approved the final version for submission.

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ED, exposure day.

Declaration of competing interest

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Bayer, Bio Products Laboratory, Opko Biologics, Pfizer and Shire. Advisory boards, honoraria for consultancy/lectures: Alnylam, Bayer, CSL Behring, Opko Biologics, Pfizer, Shire and Roche. Rolf Ljung: Advisory board or data safety monitoring committees: CSL Behring, Pfizer, Sobi, Shire, Bioverativ (last 5 years) and speaker's fees from Bayer, Shire, Novo Nordisk, Pfizer and Sobi (last 5 years).

Luminita Rusen reports no conflict of interest.

Bryce Kerlin: has served as an advisory board member for Bayer HealthCare and has received research support from Novo Nordisk A/S and CSL Behring Foundation for Research and Advancement of Patient Health.

Victor Blanchette: Member of data safety monitoring boards for Octapharma and Shire. Received fees for participation in advisory boards/education events for Bayer HealthCare, Bioverativ, Novo Nordisk, Roche, Shire and Spark Therapeutics. Recipient of research grants from Bayer HealthCare, Bioverativ and Shire.

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Horst Beckmann, Despina Tseneklidou-Stoeter, and Nikki Church are employees of Bayer.

Appendix 1

Treatment efficacy rating by the patient or caregiver

- Excellent: abrupt pain relief and/or improvement in signs of bleeding with no additional infusion administered
- Good: definite pain relief and/or improvement in signs of bleeding, but possibly requiring more than one infusion for complete resolution
- Moderate: probable or slight improvement in signs of bleeding, with at least one additional infusion for complete resolution
- Poor: no improvement at all between infusions or condition worsens

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