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BAY 81-8973 Demonstrates Long-Term Safety and Efficacy in Children With Severe Haemophilia A: Results From the LEOPOLD Kids Extension Study

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ABSTRACT

Objectives: To report the long-term safety and efficacy of BAY 81-8973 in the LEOPOLD Kids extension phase.

Methods: Patients received BAY 81-8973 (25–50 IU/kg) at least twice weekly. The primary endpoint was safety, assessed in all patients who entered the extension phase ($n = 82$). Efficacy endpoints were assessed in patients without high-titre inhibitors/immune tolerance induction ($n = 67$).

Results: Children ($n = 82$) received BAY 81-8973 for a median of 3.1 years per patient and a median of 405 exposure days per patient. Long-term BAY 81-8973 treatment was well tolerated, with no cases of de novo inhibitor development in the extension phase. Annualised bleeding rates (ABRs) within 48 h of prophylaxis were low for all bleeds (median [IQR], 0.7 [0–1.9]; mean, 1.4 [SD, 2.1]) and for joint bleeds (median [IQR], 0 [0–0.7]; mean, 0.5 [SD, 1.1]) ($n = 67$). Twenty-one of 67 patients (31.3%) had zero bleeds within 48 h of prophylaxis; the treatment response was 'good'/'excellent' in 87.9% of bleeds, and most bleeds resolved with ≤2 BAY 81-8973 infusions (83.5%).

Conclusion: Long-term BAY 81-8973 treatment is well tolerated and maintains low ABRs for all bleeds and joint bleeds in children with severe haemophilia A.

Trial Registration: ClinicalTrials.gov identifier: NCT01311648

1 | Introduction

Haemophilia A is caused by factor VIII (FVIII) deficiency and characterised by spontaneous bleeding that mainly occurs in joints, muscles and soft tissues [1]. People with untreated, recurrent joint and muscle bleeding are prone to serious musculoskeletal complications related to the development of chronic arthropathy, which causes pain, deformity and disability [2]. The primary treatment priority in haemophilia A is therefore to prevent bleeds in order to preserve long-term joint function and structure [1]. This is achieved through early initiation of long-term, regular prophylactic treatment, which aims to prevent haemarthroses and other bleeds, maintain musculoskeletal health, improve quality of life and reduce the need for both hospitalisation and surgical orthopaedic interventions in the future [1]. Prophylaxis initiated before the age of 3 years (primary prophylaxis) is the current standard of care for patients with a severe bleeding phenotype [1, 3].

While the prophylaxis landscape has increasingly shifted towards the use of extended half-life (EHL) FVIII products, standard half-life (SHL) treatments continue to play an important role in haemophilia management. Considerations such as resource and insurance coverage limitations, variable access to EHL FVIII products around the world, and patient or parent preference for established treatments ensure that SHL FVIII products remain a valuable treatment option in many countries and certain patient populations. BAY 81-8973 (Kovaltry) is an unmodified, full-length, recombinant human FVIII approved in 2016 for prophylaxis, on-demand treatment and perioperative management in patients with haemophilia A [4, 5]. While BAY 81-8973 has a primary amino acid sequence identical to that of sucrose-formulated recombinant FVIII (rFVIII-FS; Kogenate FS), it is manufactured using advanced technologies to eliminate human- and animal-derived raw materials, reduce production steps, and enhance pathogen safety [6, 7]. Like rFVIII-FS, BAY 81-8973 is manufactured in a baby hamster kidney (BHK) cell line, but with the addition of human heat shock protein 70 (HSP70), which facilitates protein folding and which may enhance FVIII expression [6]. The PK profile of BAY 81-8973 is non-inferior to that of rFVIII-FS (Kogenate FS/Kogenate) and superior when compared with antihaemophilic factor (recombinant) plasma/albumin-free method (rAHF-PFM; Advate) [7, 8], with a similar half-life across all ages and ethnic groups [8].

The LEOPOLD clinical trial programme has established the efficacy and safety of prophylaxis with BAY 81-8973 in previously treated patients (PTPs) of all ages with severe haemophilia A [9–13]. In the main phase of the two-part LEOPOLD Kids study, BAY 81-8973 was well tolerated and effective in paediatric PTPs (Part A) [10] and showed comparable safety and efficacy to other FVIII products of the same class in previously untreated/minimally treated children (PUPs/MTPs; Part B) [14]. Patients who completed ≥ 50 exposure days (EDs) in the main phase of LEOPOLD Kids were invited to participate in an optional extension phase to allow observation for an additional ≥ 50 EDs per patient. Interim results of the extension phase provided initial evidence supporting the long-term use of BAY 81-8973 when given at least twice weekly to PTPs aged ≤ 12 years ($n = 46$) [15]. Here, we report final results from the LEOPOLD Kids extension phase and describe long-term safety and efficacy data for paediatric PTPs and PUPs/MTPs followed for up to 6.4 years.

2 | Methods

2.1 | Study Design

LEOPOLD Kids was a Phase 3, multicentre, open-label, uncontrolled study to demonstrate the safety and efficacy of treatment with BAY 81-8973 for prophylaxis, treatment of breakthrough bleeds, and surgery in children with severe haemophilia A. The extension phase of LEOPOLD Kids was conducted at 45 haemophilia treatment centres in 18 countries (Argentina, Austria, Bulgaria, Canada, Denmark, Hungary, Ireland, Israel, Italy, Latvia, Lithuania, Mexico, Norway, Poland, Romania, Russian Federation, Spain, USA). All patients in the extension phase received regular prophylaxis with BAY 81-8973 (25–50 IU/kg) at least twice weekly; BAY 81-8973 was also used for breakthrough bleeds and surgery at the investigator's discretion. Dosing for surgery was to follow the standard practice used for Kogenate FS/Kogenate. Minor surgery was defined as any procedure that did not involve general anaesthesia and/or respiratory assistance (e.g., minor dental extractions, abscess incision and drainage, simple excisions). Major surgery was any procedure involving general anaesthesia and/or respiratory assistance in which a major body cavity was penetrated or exposed, or in which a substantial impairment of physical or physiological function was produced (e.g., laparotomy, thoracotomy, craniotomy, fracture).

During the extension phase, parents or caregivers recorded all bleeding events and treatment information in electronic patient diaries (EPDs). Site visits took place every six months (or more frequently for patients who developed inhibitors), but patients and their parents/caregivers interacted with investigators on a monthly basis to verify and complete the EPD and provide information on concomitant medications and adverse events (AEs).

The study protocol and amendments were reviewed and approved by all relevant independent ethics committees or institutional review boards. The study was conducted in accordance with all local and regulatory requirements, the Declaration of Helsinki and the International Council for Harmonisation (ICH) Good Clinical Practice guidelines. Written informed consent was provided by parents or legal representatives.

2.2 | Patients

Detailed inclusion and exclusion criteria for LEOPOLD Kids have been previously published [10, 14]. In brief, patients in Part A of the main phase were PTPs aged ≤ 12 years with ≥ 50 previous EDs to any FVIII product at study initiation, while those in Part B were PUPs/MTPs aged < 6 years with no or ≤ 3 previous EDs at study initiation. Patients who reached ≥ 50 EDs in Part A or Part B of the main phase were invited to participate in the extension phase for an additional ≥ 50 EDs.

2.3 | Safety Assessments

The primary objective of the LEOPOLD Kids extension phase was to assess the long-term safety of BAY 81-8973. Adverse events and serious AEs (SAEs) were monitored at each study visit (i.e., every 6 months) and assessed in terms of severity and relationship to study drug. The development of inhibitors, defined as an inhibitor value of ≥ 0.6 Bethesda units [BU]/mL (as measured by the Nijmegen-modified Bethesda assay at a central laboratory, and confirmed in two separate plasma samples), was considered to be an SAE. Inhibitor assessment was conducted at every study visit during the extension phase (or more frequently for patients who developed an inhibitor), including the point at which patients reached approximately 50 EDs in the extension phase (i.e., 100 EDs over the main plus extension phases). Other safety variables included vital signs and physical examination (body weight and height), assessed at every study visit.

2.4 | Efficacy Assessments

Data for the assessment of efficacy variables were collected throughout the extension phase. The primary efficacy variable was the annualised number of total bleeds occurring within 48 h of a prophylaxis infusion; the annualised numbers of joint, spontaneous, and trauma bleeds occurring within 48 h after a prophylaxis infusion were also calculated.

Additional efficacy variables included the following: annualised numbers of total, joint, spontaneous and trauma bleeds independent of time of last infusion; number of treatments required to control bleeds; patient/caregiver assessment of treatment response, categorised as excellent (abrupt pain relief and/or improvement in signs of bleeding, with no additional infusions 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), or poor (no improvement at all between infusions, or condition worsens); FVIII consumption; haemostatic outcome of surgeries (blood loss, transfusion); FVIII recovery; and proportion of patients without bleeds.

2.5 | Incremental FVIII Recovery

FVIII recovery was assessed in conjunction with planned prophylaxis infusions, using the patient's usual dose. Blood samples for recovery assessment in patients who were not actively bleeding were collected pre-infusion and 20–30 min post-infusion at the first extension visit (6 months after the start of the extension) and at the final visit. Additional samples could be obtained at any time from patients who developed an inhibitor. Pre-infusion samples were to be collected at least 48 h after the previous BAY 81-8973 infusion. Plasma FVIII:C was measured in the central laboratory using a chromogenic assay (Biophen FVIII:C kit [HYPHEN BioMed, France; Ref. 221402]) [16].

2.6 | Analysis Sets

Data analysis was based on the intent-to-treat population, which comprised all patients who entered the extension study and who received at least one dose of the study drug during the entire study period (main plus extension phases). Safety analysis (the primary objective) was based on the entire intent-to-treat population and therefore included all patients who entered the extension period, including patients with high-titre inhibitors and those undergoing ITI. Hereafter, this group is referred to as the 'safety group' ($n = 82$). It should be noted that the safety group included three patients who did not receive the study drug during the extension period (all three patients had high-titre inhibitors but did not undergo planned ITI in the extension phase). Efficacy analyses were also based on the intent-to-treat population, but excluded all patients with high-titre inhibitors and those undergoing ITI. In this group, hereafter referred to as the 'efficacy group' ($n = 67$), the 15 excluded patients comprised 12 patients with high-titre ($n = 11$) or low-titre ($n = 1$) inhibitors who received ITI (efficacy outcomes for these patients are reported elsewhere [14]) and the three patients described above who did not receive the study drug during the extension phase (all had high-titre inhibitors but did not receive ITI). The efficacy group included three patients who had low-titre inhibitors at entry into the extension phase, all of whom became inhibitor-negative within 6 months of initial detection.

2.7 | Statistical Analysis

The patient sample size enrolled in the extension study was consistent with the regulatory requirements of the European Medicines Agency. All safety and efficacy analyses were based on the extension phase only, and data were summarised using descriptive statistics and calculated using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA). As both the safety group ($n = 82$) and efficacy group ($n = 67$) were based on the intent-to-treat population, all patients were included in data analyses even if they did not reach ≥ 50 EDs in the extension phase (i.e., ≥ 100 EDs overall, across the main plus extension phases).

3 | Results

3.1 | Patients

Of 82 patients who entered the extension phase, 46 were PTPs and 36 were PUPs ($n = 33$) or MTPs ($n = 3$). Patient demographics and clinical characteristics for this group are shown in Table 1. At the start of the extension phase, the overall median (range) patient age was 4 (1–12) years, with median (range) ages of 7 (2–12) years and 2 (1–4) years among PTPs and PUPs/MTPs, respectively. Demographics and clinical characteristics were similar among patients in the efficacy group ($N = 67$) (Table S1).

In total, 70 patients completed the extension phase, with 12 discontinuing after a median of 15.8 (range, approximately 5–38) months (Figure 1) due to ITI failure ($n = 3$), inhibitor management outside the study ($n = 3$), family decision ($n = 1$), physician

TABLE 1 | Study population in the extension phase: Patient demographics and clinical characteristics (safety group[a]).

	PTPs	PUPs/MTPs	Total
	***N*=46**	***N*=36**	***N*=82**
Age at the start of the extension phase, years			
Mean (SD)	7.6 (3.1)	1.7 (0.7)	5.0 (3.8)
Median (range)	7.0 (2.0–12.0)	2.0 (1.0–4.0)	4.0 (1.0–12.0)
Race,[b] *n* (%)			
White	43 (93.5)	32 (88.9)	75 (91.5)
Black	3 (6.5)	0	3 (3.7)
American Indian or Alaska native	0	1 (2.8)	1 (1.2)
White, American Indian or Alaska native	0	1 (2.8)	1 (1.2)
Not reported	0	2 (5.6)	2 (2.4)
BMI at the start of the extension phase, kg/m^2			
N	46	30	76
Mean (SD)	16.2 (2.6)	16.9 (1.5)	16.5 (2.3)
Median (range)	15.7 (12.6–25.0)	16.7 (14.4–21.1)	16.4 (12.6–25.0)
Age at diagnosis,[b] months			
N	46	32	78
Mean (SD)	8.2 (8.4)	6.7 (6.8)	7.6 (7.8)
Median (range)	6.5 (0–42)	6.5 (0–32)	6.5 (0–42)
Presence of target joints,[b] *n* (%)			
Yes	14 (30.4)	1 (2.8)	15 (18.3)
No	32 (69.6)	35 (97.2)	67 (81.7)
Number of target joints,[b] *n* (%)			
0	32 (69.6)	35 (97.2)	67 (81.7)
1	9 (19.6)	1 (2.8%)	10 (12.2)
2	3 (6.5)	0	3 (3.7)
3	1 (2.2)	0	1 (1.2)
4	1 (2.2)	0	1 (1.2)
Number of bleeds in previous 12 months[b]			
Mean (SD)	7.9 (12.5)	1.1 (1.7)	4.9 (10.0)
Median (range)	4.5 (0.0–55.0)	0.0 (0.0–7.0)	1.00 (0.0–55.0)
Number of joint bleeds in the previous 12 months[b]			
Mean (SD)	3.9 (6.5)	0.1 (0.2)	2.2 (5.2)
Median (range)	0.0 (0.0–33.0)	0.0 (0.0–1.0)	0.0 (0.0–33.0)

Abbreviations: BMI, body mass index; MTPs, minimally treated patients; PTPs, previously treated patients; PUPs, previously untreated patients; SD, standard deviation.
[a]Safety group: all patients who entered the extension phase and who had at least one dose of study drug during the entire study period (main + extension phases).
[b]Assessed at the start of the main study (Part A [PTPs] or Part B [PUPs/MTPs]).

decision ($n=1$), long travel to the assessment centre ($n=1$), diagnosis with von Willebrand disease ($n=1$), incorrect visit planning ($n=1$) and withdrawal by patient ($n=1$). The discontinuation rate was higher among PUPs/MTPs (11 [30.6%]) than among PTPs (1 [2.2%]).

3.2 | Treatment Duration and Exposure

In the safety group ($n=82$), the median (range) time in the extension phase was 3.1 (0.3–6.4) years per patient (mean, 3.0 [SD, 1.8] years), and the median (range) number of EDs

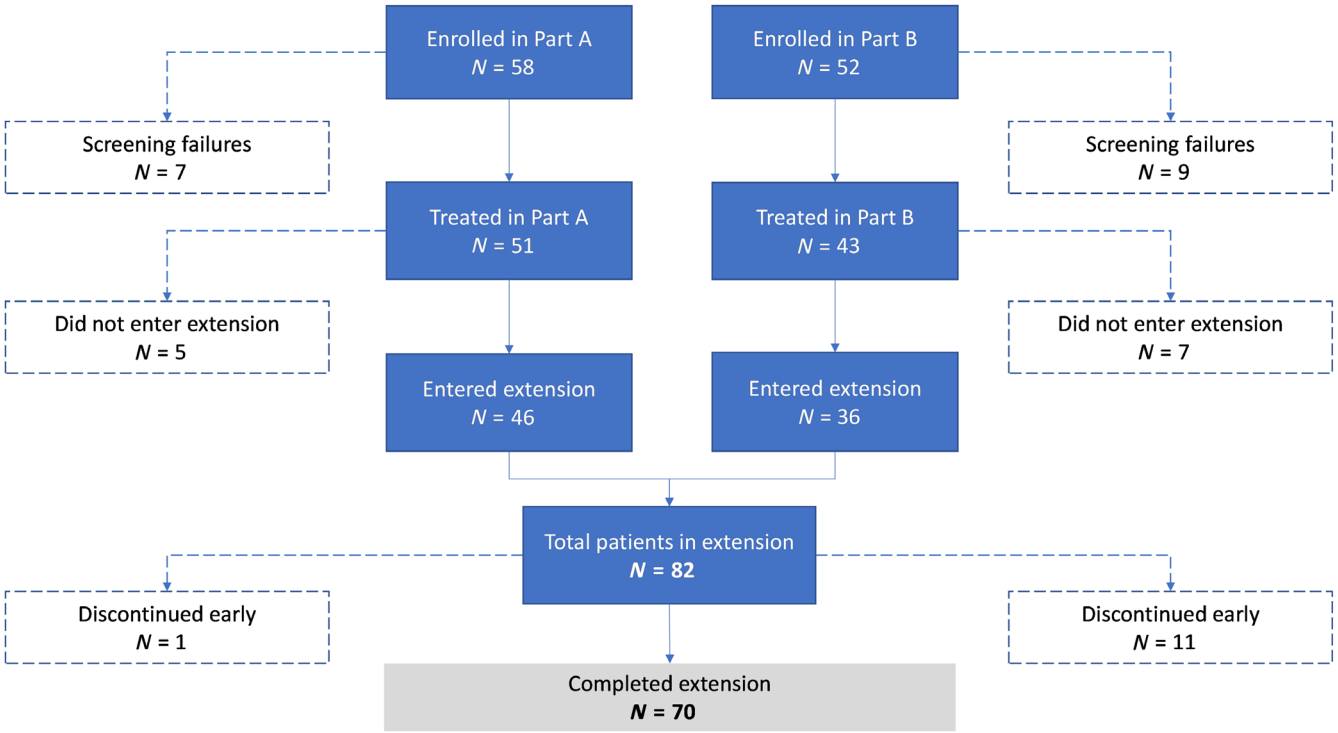

FIGURE 1 | Patient disposition.

was 405 (0–1171) per patient (mean, 415 [SD, 286] EDs). In the efficacy group ($n = 67$), patients remained in the extension phase for a median (range) of 3.8 (0.3–6.4) years per patient (mean, 3.3 [SD, 1.8] years) and accrued a median (range) of 421 (41–1171) EDs per patient (mean, 450 [SD, 293] EDs). Overall, 75/82 (91.5%) patients in the safety group and 63/67 (94.0%) patients in the efficacy group achieved ≥ 50 EDs in the extension phase. Furthermore, most patients in both the safety group (76/82 [92.7%]) and the efficacy group (64/67 [95.5%]) achieved the goal of ≥ 100 EDs across the entire study duration (main plus extension phases).

In the efficacy group ($n = 67$), most patients (63/67 [94.0%]) were receiving prophylaxis with BAY 81-8973 at least twice weekly by the end of the extension phase: the majority had prophylaxis three times per week (27/67 [40.3%]) or twice per week (23/67 [34.3%]), with the remainder receiving study drug every other day (13/67 [19.4%]), once weekly (3/67 [4.5%]), or every 4 days (1/67 [1.5%]). In total, 30 449 infusions of BAY 81-8973 were administered in the efficacy group ($n = 67$) during the extension phase, most of which (29395) were prophylactic. The median (range) dose per prophylaxis infusion was 33.9 (16–57) IU/kg (mean, 34.0 [SD, 8.2] IU/kg).

3.3 | Safety

Adverse events were assessed in the safety group ($n = 82$). In total, 75/82 (91.5%) patients experienced AEs, with most reporting that the AEs were of mild or moderate severity (56/82 [68.3%]). While 37/82 (45.1%) patients experienced SAEs, all such events were more common in patients who developed a high-titre inhibitor during the main phase (Table 2). Notably, there were no new cases of inhibitor development during the extension. Serious bleeding events were predominantly observed as isolated cases, and the most common type of serious bleeding event was haemarthrosis (reported in 4 [4.9%] patients). None of these serious bleeding events were related to the study drug or led to discontinuation.

Three of 82 (3.7%) patients experienced three SAEs that were assessed by the investigator as related to study drug. Two of these events (hospitalisation associated with central venous catheterisation prior to ITI treatment in two PUPs/MTPs with high-titre inhibitors) occurred approximately 2 months after the last dose of BAY 81-8973 and are therefore not considered to be truly related to study treatment. The third study drug-related AE, development of a low-titre, transient inhibitor in a 13-year-old PTP, has been previously reported in the interim analysis [15]. It was concluded that this transient inhibitor, which occurred concurrently with acute infection, was probably caused by cross-reactivity with anticardiolipin antibodies [17–19].

There were no deaths, no study drug discontinuations due to AEs, and no clinically relevant changes in vital signs.

3.4 | Efficacy

3.4.1 | Annualised Number of Bleeds Within 48 h After a Prophylaxis Infusion

In the efficacy group ($n = 67$), annualised bleeding rates (ABRs) for total and joint bleeds remained low throughout the extension phase (Table 3). Among all 67 patients, the median (IQR) ABR for total bleeds within 48 h after a prophylaxis infusion was 0.7 (0–1.9), and the respective mean (SD) ABR was 1.4 (2.1). A total of 150 joint bleeds occurred, with a median (IQR) ABR of 0 (0–0.7) (mean, 0.5

TABLE 2 | Summary of adverse events in the extension phase (safety group[a]).

	PTPs	PUPs/MTPs	Total
	N = 46	*N* = 36	*N* = 82
Safety summary, *n* (%)			
Number of patients with ≥ 1 AE	46 (100.0)	29 (80.6)	75 (91.5)
AEs by severity			
Mild	11 (23.9)	11 (30.6)	22 (26.8)
Moderate	25 (54.3)	9 (25.0)	34 (41.5)
Severe	10 (21.7)	9 (25.0)	19 (23.2)
Number of patients with ≥ one AE related to study drug	1 (2.2)[b]	2 (5.6)[c]	3 (3.7)
Number of patients with ≥ one SAE	23 (50.0)	14 (38.9)	37 (45.1)
Number of patients who discontinued due to AEs	0	0	0
Most common AEs, *n* (%)[d]			
Nasopharyngitis	14 (30.4)	9 (25.0)	23 (28.0)
Pyrexia	8 (17.4)	11 (30.6)	19 (23.2)
Cough	9 (19.6)	3 (8.3)	12 (14.6)
Vomiting	4 (8.7)	6 (16.7)	10 (12.2)
Tonsillitis	10 (21.7)	0	10 (12.2)
Limb injury	9 (19.6)	1 (2.8)	10 (12.2)
Upper respiratory tract infection	6 (13.0)	3 (8.3)	9 (11.0)
Viral infection	7 (15.2)	2 (5.6)	9 (11.0)
Most common SAEs, *n* (%)[e]			
Central venous catheterisation	2 (4.3)	4 (11.1)	6 (7.3)
Vascular device infection	2 (4.3)	3 (8.3)	5 (6.1)
Haemarthrosis	1 (2.2)	3 (8.3)	4 (4.9)

Abbreviations: AE, adverse event; ITI, immune tolerance induction; MTPs, minimally treated patients; PTPs, previously treated patients; PUPs, previously untreated patients; SAE, serious adverse event.
[a]Safety group: All patients who entered the extension phase and who had at least one dose of study drug during the entire study period (main + extension phases).
[b]As previously reported in the interim analysis [15], one 13-year-old PTP developed a low-titre, transient inhibitor concurrent with acute infection. This transient inhibitor was likely caused by cross-reactivity with anticardiolipin antibodies.
[c]Two PUPs/MTPs with high-titre inhibitors experienced hospitalisation associated with central venous catheterisation prior to ITI treatment. However, both of these events occurred approximately 2 months after the last dose of BAY 81-8973 and are therefore not considered to be truly related to study treatment.
[d]Occurring in ≥ 10% of patients.
[e]Occurring in ≥ 5% of patients. All SAEs occurred more frequently in patients with high titre inhibitors vs. those without: 4 (33.3%) versus 2 (3.0%) for central venous catheterisation, 3 (25.0%) versus 2 (3.0%) for vascular device infection, and 3 (25.0%) versus 1 (1.5%) for haemarthrosis.

TABLE 3 | Bleeds within 48 h after prophylaxis infusion in the extension phase (efficacy group[a]).

	PTPs	PUPs/MTPs	Total
	N = 46	*N* = 21	*N* = 67
ABR for total bleeds occurring within 48 h after prophylaxis infusion			
Median (IQR)	1.0 (0.2–1.9)	0.3 (0.0–1.4)	0.7 (0.0–1.9)
Mean (SD)	1.5 (2.2)	1.2 (2.0)	1.4 (2.1)
ABR for spontaneous bleeds within 48 h after prophylaxis infusion			
Median (IQR)	0.0 (0.0–0.7)	0.0 (0.0–0.0)	0.0 (0.0–0.4)
Mean (SD)	0.6 (1.4)	0.1 (0.2)	0.4 (1.2)
ABR for trauma bleeds within 48 h after prophylaxis infusion			
Median (IQR)	0.4 (0.0–1.2)	0.0 (0.0–1.0)	0.3 (0.0–1.2)
Mean (SD)	0.9 (1.1)	0.7 (1.4)	0.8 (1.2)
ABR for joint bleeds within 48 h after prophylaxis infusion			
Median (IQR)	0.2 (0.0–1.1)	0.0 (0.0–0.0)	0.0 (0.0–0.7)
Mean (SD)	0.7 (1.2)	0.2 (0.3)	0.5 (1.1)

Abbreviations: ABR, annualised bleeding rate; IQR, interquartile range; MTPs, minimally treated patients; PTPs, previously treated patients; PUPs, previously untreated patients; SD, standard deviation.
[a]Efficacy group: all patients who entered the extension phase and who had at least one dose of study drug during the entire study period (main + extension phases), excluding patients with high-titre inhibitors and/or those receiving immune tolerance induction treatment.

[SD, 1.1]) within 48 h of a prophylaxis infusion. There were more trauma-related bleeds (*n* = 173) than spontaneous bleeds (*n* = 114), with median (IQR) (mean [SD]) ABRs of 0.3 (0.0–1.2) (0.8 [1.2]) and 0.0 (0.0–0.4) (0.4 [1.2]), respectively (Table 3). Almost one-third of patients (21/67 [31.3%]) did not experience a bleed within 48 h of prophylaxis during the extension phase.

3.4.2 | Annualised Number of Bleeds Independent of the Last Prophylaxis Infusion

When analysed independently of the time of last infusion, the median (IQR) total bleed ABR in the efficacy group (*n* = 67) was 1.9 (0.3–3.9) (mean, 2.7 [SD, 3.7]) (Table 4). For joint bleeds assessed independently of the last infusion (*n* = 233), median (IQR) ABRs remained low throughout the extension for all patients (0.4 [0.0–1.7]; mean, 0.9 [SD, 1.3]). Again, trauma-related bleeds (*n* = 271; median [IQR] ABR, 0.6 [0–1.9]; mean, 1.3 [SD, 1.7]) were more common than spontaneous bleeds (*n* = 183; median [IQR] ABR, 0 [0–0.8]; mean, 0.7 [SD, 1.5]) (Table 4). In total, 14/67 (20.9%) patients did not have any bleeds at any time during the extension phase.

3.4.3 | Treatment of Bleeds

Patients in the efficacy group (*n* = 67) experienced a total of 531 bleeds during the extension phase (PTPs, *n* = 423 bleeds; PUPs/MTPs, *n* = 108 bleeds), the majority of which were mild or moderate in severity (498 [93.8%]). Of 233 joint bleeds overall, most

TABLE 4 | Annualised bleeding rate by bleed type in the extension phase (efficacy group[a]).

	PTPs	PUPs/MTPs	Total
	***N*=46**	***N*=21**	***N*=67**
Patients with ≥1 bleed, *n* (%)			
No	9 (19.6)	5 (23.8)	14 (20.9)
Yes	37 (80.4)	16 (76.2)	53 (79.1)
ABR for total bleeds			
Median (IQR)	1.9 (0.3–3.5)	1.9 (0.5–4.0)	1.9 (0.3–3.9)
Mean (SD)	2.4 (2.7)	3.6 (5.4)	2.7 (3.7)
ABR for spontaneous bleeds			
Median (IQR)	0.2 (0.0–1.1)	0.0 (0.0–0.3)	0.0 (0.0–0.8)
Mean (SD)	0.9 (1.7)	0.4 (0.9)	0.7 (1.5)
ABR for traumatic bleeds			
Median (IQR)	0.7 (0.0–1.8)	0.5 (0.0–1.9)	0.6 (0.0–1.9)
Mean (SD)	1.3 (1.6)	1.4 (2.1)	1.3 (1.7)
ABR for joint bleeds			
Median (IQR)	0.6 (0.0–1.8)	0.0 (0.0–1.7)	0.4 (0.0–1.7)
Mean (SD)	1.1 (1.4)	0.7 (0.9)	0.9 (1.3)

Abbreviations: ABR, annualised bleeding rate; IQR, interquartile range; MTPs, minimally treated patients; PTPs, previously treated patients; PUPs, previously untreated patients; SD, standard deviation.
[a]Efficacy group: all patients who entered the extension phase and who had at least one dose of study drug during the entire study period (main + extension phases), excluding patients with high-titre inhibitors and/or those receiving immune tolerance induction treatment.

occurred in PTPs (209 [89.7%] vs. 24 [10.3%] in PUPs/MTPs). Joint bleeds were also the most common bleed type in PTPs, comprising almost half of all bleeds in these children (209/423 [49.4%]). In contrast, in PUPs/MTPs, joint bleeds (24/108 [22.2%]) were considerably less frequent than skin/mucosa bleeds (59/108 [54.6%]).

Of the 531 bleeds, 59 did not require treatment, and 472 were treated with BAY 81-8973 at a median (range) dose of 35.5 (18–67) IU/kg (mean, 35.6 [SD, 10.0] IU/kg). Among the 472 treatment-requiring bleeds in the whole efficacy group, trauma-related bleeds were more common (271 [57.4%]) than spontaneous bleeds (183 [38.8%]). Trauma bleeds were also more prevalent than spontaneous bleeds in both PTPs (215/401 [53.6%] vs. 172/401 [42.9%]) and PUPs/MTPs (56/71 [78.9%] vs. 11/71 [15.5%]). Most of the 472 bleeds treated with BAY 81-8973 were resolved with ≤two infusions (394 [83.5%]), while the remaining bleeds required ≥three infusions (78 [16.5%]); response to treatment was rated by patients/caregivers as 'good' or 'excellent' in 87.9% of assessed bleeds.

3.4.4 | Surgery

Eleven major surgeries (as defined in the Section 2) were performed during the extension. Six patients each underwent one major procedure (removal of a central venous access device [CVAD]; repair of right anterior CSF leak and encephalocele; appendectomy; adenotonsillectomy; CVAD insertion and arteriovenous fistula creation [originally categorised as a minor procedure and later reclassified as major]). Haemostasis was rated good or excellent for all three surgeries for which assessment was available, and there were no surgical complications or requirements for blood transfusion. Another patient underwent five major procedures, all related to CVAD insertion or removal, with excellent/good ($n=4$ surgeries) or moderate ($n=1$) haemostatic outcomes.

In addition, 36 minor procedures (as defined in the Section 2) were performed. Most were CVAD-related procedures (22 procedures in 13 patients) or dental procedures/tooth extractions (five procedures in five patients). The remaining nine procedures, each of which was performed in one patient, were bilateral tympanostomy tube placement, arthroscopy, nasal polyp removal, gastroscopy, esophagogastroduodenoscopy and biopsy, endopleural catheter placement, cardiac catheterisation and removal of foreign bodies, extirpation of subcutaneous chest granuloma and laser coagulation. Surgical haemostasis with BAY 81-8973 was rated as good or excellent for all but one procedure, rated moderate (CVAD removal in a patient with high-titre inhibitor receiving ITI), and no blood transfusions were required intraoperatively.

3.4.5 | Incremental FVIII Recovery

FVIII recovery data were available for 25 patients without an inhibitor. The median (IQR) trough level was 1.24 (0.75–3.31) IU/dL, and the median (IQR) recovery was 1.66 (1.49–1.85) IU/dL per IU/kg.

4 | Discussion

Consistent with the interim analysis [15], final results from the LEOPOLD Kids extension phase show that BAY 81-8973 is well tolerated and effective when used for long-term prophylaxis in children with severe haemophilia A. Patients in the extension phase were treated for up to 6.4 years (median, 3.1 years) per patient and accumulated a median of 405 EDs per patient, with most receiving prophylaxis infusions at least twice weekly.

Notably, there were no cases of de novo inhibitor development during the extension in any patients, including PUPs who did not develop an inhibitor during Part B of the main phase. There were no serious unexpected AEs and no new safety concerns: most AEs were mild or moderate in severity, and the most frequently reported events were those commonly observed in children with haemophilia A. Most of the observed SAEs were associated with central venous catheterisation or bleeding and predominantly affected patients with high-titre inhibitors; none led to study discontinuation. Overall, safety data from the LEOPOLD Kids extension phase are consistent with those expected for this class of FVIII product in the paediatric population.

Although efficacy assessment was not the primary endpoint of the extension phase, bleeding was assessed using several different parameters. Final extension phase data show that BAY

81-8973 maintained a median (mean) ABR of 0.7 (1.4) for total bleeds within 48 h after a prophylaxis infusion. When data were analysed for PTPs and PUPs/MTPs, median (mean) ABRs for total bleeds within 48 h after prophylaxis were 1.0 (1.5) and 0.3 (1.2), respectively. These ABRs are similar to those previously reported for PTPs at the extension interim analysis (median [mean] ABR of 1.0 [1.5] for the main phase + extension phase up to the interim analysis) [15] and for PUPs during the main phase (median [mean] ABR of 0 [0.9]) [14], indicating that bleeding protection was maintained long-term. Almost one-third of patients overall (31.3%) did not experience any bleeds during the extension phase within 48 h after a prophylaxis infusion, and bleeds that did occur were more often trauma-related than spontaneous. Furthermore, BAY 81-8973 was efficacious for the treatment of bleeds: 83.5% of bleeds were successfully treated with ≤ 2 infusions, and response to treatment was 'good' or 'excellent' for 87.9% of treated bleeds. Haemostatic efficacy was also rated as 'good' or 'excellent' for all evaluable major surgeries and all but one minor surgery.

It is well established that effective prevention of joint bleeds through prophylaxis is crucial to help preserve joint health [20]. Protection against joint bleeds was also maintained long-term in children treated with BAY 81-8973 in LEOPOLD Kids and its extension phase, as demonstrated by consistently low joint bleed ABRs throughout the entire study. Among PUPs/MTPs, the median (mean) joint bleed ABR within 48 h post-infusion was 0 (0.2) in both the main phase [14] and the extension phase; as the vast majority of these patients (95.2%) did not have target joints at study entry, these data show that long-term primary prophylaxis with BAY 81-8973 may help to preserve joint health and function in young children with pristine or near-pristine joints at the start of treatment. BAY 81-8973 treatment also maintained low joint bleed rates among PTPs over time (median [mean] joint bleed ABR within 48 h of a prophylaxis infusion, 0.3 [0.7] at the extension interim analysis [15] vs. 0.2 [0.7] at the final extension analysis), despite almost one-third (30.4%) of these patients having target joints at baseline. This pattern of sustained joint bleed protection over time was maintained when data were analysed independently of last infusion: median (mean) joint bleed ABRs at any time were 0 (0.9) and 0 (0.7) for PUPs/MTPs in the main [14] and extension phases, respectively, and 0.7 (mean not available) versus 0.6 (1.1) for PTPs at the extension interim [15] versus final analyses, respectively.

As previously noted [15], one limitation of this study is that it was an open-label, extension, uncontrolled clinical trial. Additionally, it would have been interesting to monitor physical activity in order to assess the correlation between joint bleeds and activity levels. Nonetheless, with a median follow-up period of 3.1 years in a large patient group with documented treatment regimens, the LEOPOLD Kids study provides robust, long-term data regarding the benefits of prolonged prophylaxis on ABR and joint ABR in paediatric patients in real-life settings. This is notable in a treatment era that has become increasingly complex, partly due to the availability of the non-factor therapy emicizumab and subsequent shifts in the current treatment paradigm [1, 20, 21]. Emicizumab has shown effective bleeding prevention in both clinical trials and real-world experience; however, there are limited data available on long-term safety and efficacy data in neonates and PUPs, and there is currently a lack of data on joint outcomes associated with emicizumab use [22–24]. In contrast, the use of prophylaxis with FVIII concentrates has been well characterised by decades of clinical trial and real-world evidence, and the efficacy of FVIII prophylaxis in reducing joint bleeds and preventing or delaying arthropathy is well established [25, 26]. The LEOPOLD Kids study adds to this wealth of accumulated evidence by demonstrating that protection against joint bleeds is also maintained long-term in children treated with BAY 81-8973 as primary prophylaxis.

5 | Conclusion

In an increasingly complex and diverse treatment landscape, where experience and data are limited for new and emerging therapeutic options, data from the LEOPOLD Kids study confirm the suitability and efficacy of BAY 81-8973 when used for long-term prophylaxis in children with severe haemophilia A. In the LEOPOLD Kids extension phase, BAY 81-8973 was well tolerated and efficacious when used to prevent and treat bleeds over a median of 3.1 years (median, 405 EDs) per patient in PTPs and PUPs/MTPs initially aged ≤ 12 years. There were no new nor major safety concerns, and the long-term safety and tolerability profile of BAY 81-8973 was consistent with previous experience with this class of FVIII product in paediatric patients. Children typically require three infusions per week of an SHL concentrate, even though many in the LEOPOLD Kids study maintained low ABRs with at least twice-weekly dosing. Additionally, most breakthrough bleeds were successfully resolved with ≤ two infusions. Long-term prophylaxis with BAY 81-8973 also maintained very low joint ABRs, which has crucial implications for long-term joint health.

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Conflicts of Interest

R.L. has during the last three years received consultancy or speaker's fee from Idogen AB, Sobi, Novo Nordisk, Takeda, Sanofi, Bayer; none of these is related to the present work. A.K.C.C. has conducted clinical trials for Bayer, Daiichi, Novo Nordisk, Pfizer, Sanofi, Sobi and Takeda, and has participated in advisory boards for and received speaker fees from Bayer, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi and Takeda. He has a patent on anticoagulation with ATTWILL, and received grants from I-ACT, AceAge, C17, Novo Nordisk and the Canadian Hemophilia Society. S.P.A. has received research grants from the US Department of Defence and XaTek Inc., royalties from ClotChip, has a patent with TraumaChek and has received consultancy fees from Biomarin, CSL Behring and Genentech, while his institution has received consulting fees from Sanofi Genzyme. In addition, he has participated as a member of the Data Safety Monitoring Board for the Takeda Oncology Ponatinib Phase 1/2 study and is a member of the Ohio Rare Disease Advisory Council and the FDA Blood Products Advisory Committee. M.E.M. has acted as a paid speaker/advisor/consultant for Bayer, Biomarin,

CSL Behring, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, Sobi and Takeda. J.F.C.M. is an employee of Bayer. F.V. is now an employee of ClinStat GmbH and reports consulting or advisory roles of his CRO with Bayer. AGV.B. has acted as a paid speaker for Takeda and Sanofi in educational events and is a member of data safety monitoring boards for Takeda. He is the Chair of the International Prophylaxis Group, which is funded by educational grants to the Hospital for Sick Children Foundation (Toronto, Canada) from Bayer, BioMarin, Novo Nordisk, Pfizer, Sanofi, Sobi, Roche and Takeda. B.A.K. has received research funding from Genentech and Novo Nordisk within the last three years. V.B. has received research grants from Sanofi—Genzyme, Bayer Healthcare and Takeda, and has acted as a paid speaker for Takeda, Sanofi-Genzyme, Bayer Healthcare, Novo Nordisk, Pfizer and Spark Therapeutics in Educational events. He also received royalties for the Canadian Hemophilia Outcomes Kids Life Assessment Tool (CHOKLAT). He is a member of data safety monitoring boards for Takeda and also the Chair of the International Prophylaxis Group that is funded by educational grants to the Hospital for Sick Children Foundation (Toronto, Canada) from Bayer, Biomarin, Novo Nordisk, Pfizer, Sanofi, Sobi, Roche and Takeda. S.S.T. is the chair of the Lithuanian Society of Pediatric Hematology and Oncology; she has received support from Bayer, Novo Nordisk and Roche to attend meetings and/or travel, and payment or Honoria from Bayer Novo Nordisk, Roche and Octapharma. H.G. has acted as Principal Investigator and conducted several clinical trials for different companies over the last nine years. She has received medical writing support from Sobi. G.K. has received grants from Alnylam, Bayer, BPL, Opko Biologics, Pfizer, Roche and Shire and consulting fees and/or honoraria from ASC Therapeutics, Bayer, BPL, BioMarin Pharmaceutical, CSL, Novo Nordisk, Opko Biologics, Pfizer, Takeda, Roche, Sanofi, Sobi, Spark and UniQure.

Data Availability Statement

Availability of the data underlying this publication will be determined according to Bayer's commitment to the EFPIA/PhRMA 'Principles for responsible clinical trial data sharing'. This pertains to scope, timepoint and process of data access. As such, Bayer commits to sharing upon request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the United States (US) and European Union (EU) as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the EU and US regulatory agencies on or after 1 January 2014. Interested researchers can use www.vivli.org to request access to anonymised patient-level data and supporting documents from clinical studies to conduct further research that can help advance medical science or improve patient care. Information on the Bayer criteria for listing studies and other relevant information is provided in the member section of the portal. Data access will be granted to anonymised patient-level data, protocols and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.