Received: 16 December 2020 | Revised: 5 February 2021 | Accepted: 25 February 2021

DOI: 10.1111/hae.14294

Haemophilia WILEY

ORIGINAL ARTICLE

Clinical Haemophilia

PROTECT VIII kids extension study: Long-term safety and efficacy of BAY 94-9027 (damoctocog alfa pegol) in children with severe haemophilia A

Maria Elisa Mancuso[1,2] | Tina Biss[3] | Kathelijn Fischer[4] | Monika Maas Enriquez[5] | MacGregor Steele[6] | Maria Wang[7] | Despina Tseneklidou-Stoeter[8] | Sanjay Ahuja[9] | Gili Kenet[10]

[1]Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy

[2]Center for Thrombosis and Hemorrhagic Diseases, IRCCS Humanitas Research Hospital, Milan, Italy

[3]Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK

[4]Van Creveldkliniek, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

[5]Bayer, Wuppertal, Germany

[6]Cumming School of Medicine, Alberta Children's Hospital, University of Calgary, Calgary, AB, Canada

[7]Bayer, Whippany, NJ, USA

[8]Bayer, Berlin, Germany

[9]Rainbow Hemostasis & Thrombosis Center, University Hospitals Rainbow Babies and Children's Hospital, Case Western Reserve University School of Medicine, Cleveland, OH, USA

[10]Israel National Hemophilia Center, Chaim Sheba Medical Center, Tel Hashomer, Israel & The Amalia Biron Thrombosis Research Institute, Tel Aviv University, Tel Aviv, Israel

Correspondence
Maria Elisa Mancuso, Center for Thrombosis and Hemorrhagic Diseases, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy.
Email: mariaelisa_mancuso@libero.it

Funding information
This study was funded by Bayer.

Abstract

Introduction: BAY 94-9027 (damoctocog alfa pegol; an extended half-life PEGylated recombinant factor VIII [FVIII]) demonstrated efficacy and safety in previously treated paediatric patients (PTPs) aged <12 years with severe haemophilia A in the PROTECT VIII Kids study (NCT01775618).

Aim: To evaluate the long-term safety of BAY 94-9027 in PTPs aged <12 years at enrolment.

Methods: In the PROTECT VIII Kids study, boys <12 years with severe haemophilia A were enrolled in two age cohorts (6–<12 years and <6 years) and treated prophylactically twice weekly, every 5 days or every 7 days, with BAY 94-9027 for ≥50 exposure days (EDs). Patients who had completed ≥50 EDs and ≥6 months in the main study or 12-week safety expansion study were eligible to participate in the extension. Primary safety variable was frequency of inhibitor development; main efficacy variable was annualised bleeding rate (ABR).

Results: Of 73 PTPs from the main/expansion studies, 59 (81%) entered the extension phase for a median (range) duration of 5.0 (0.4–5.9) years. Overall, 39 patients completed ≥5 years of treatment. No patients developed FVIII inhibitors/anti-PEG antibodies, and two patients aged <6 years discontinued. Median ABR for total bleeds was 1.5 (<6 years) and 1.9 (6–<12 years). Total ABR improved in the extension vs. the main study. In the last 12 months of treatment, median spontaneous ABR was 0.0 in both age groups.

Conclusions: BAY 94-9027 showed long-term safety and efficacy for the prevention and treatment of bleeds in younger and older paediatric patients with severe haemophilia A.

KEYWORDS
adolescents, children, damoctocog alfa pegol, FVIII, haemophilia A, polyethylene glycol, prophylaxis

1 | INTRODUCTION

Haemophilia A is a hereditary coagulation disorder affecting approximately 1 in 5000 males and is caused by a genetic deficiency in coagulation factor VIII (FVIII).[1,2] Regular FVIII replacement therapy is the standard treatment for patients with severe haemophilia (ie <1% FVIII activity), and either recombinant or plasma-derived FVIII may be injected intravenously as part of a prophylaxis regimen or on demand.[1,3,4] Standard FVIII products (half-life ~10–12 h) are associated with a need for frequent injections, which may prove burdensome and pose challenges to treatment adherence; therefore, various extended half-life therapeutic FVIII products have been developed.[1,4-6]

One strategy to extend the half-life of FVIII involves conjugating this protein with polyethylene glycol (PEG), thus decreasing its hepatic clearance.[7,8] BAY 94-9027 (damoctocog alfa pegol; Jivi®; Bayer) is a B-domain–deleted recombinant FVIII protein that is site-specifically conjugated with a 60 kDa PEG moiety to extend circulatory half-life.[6,7] The efficacy and safety of treatment with BAY 94-9027 for preventing and treating bleeds in adult and adolescent patients (aged 12–65 years) with severe haemophilia A were demonstrated in the Phase 2/3 PROTECT VIII study (NCT01580293)[9] and independently evaluated in a paediatric population in the Phase 3 PROTECT VIII Kids study (NCT01775618; main study), which enrolled previously treated patients (PTPs) aged <12 years with severe haemophilia A. A subsequent 12-week safety expansion study was also conducted that enrolled 12 patients aged <6 years.[10] A total of 12 patients (11 of whom were aged <6 years) discontinued due to hypersensitivity or apparent loss of efficacy. Patients in the main study were followed for a mean total of 7.8 months and patients in the expansion study for a mean total of 2.2 months. For those patients who remained (in either the main or expansion studies), BAY 94-9027 was well-tolerated and efficacious for the prevention and treatment of bleeds in a paediatric population. No FVIII inhibitors developed in any patients enrolled in either study.[10]

The primary objective of the optional PROTECT VIII Kids extension study was to evaluate the long-term safety of BAY 94-9027 in PTPs aged <12 years over at least 100 exposure days (EDs). Final safety and efficacy data following more than 5 years of observation are reported.

2 | MATERIALS AND METHODS

2.1 | Patients

Eligibility for inclusion in the extension study was based on completion of the main study or the expansion study, with informed consent for the extension phase. Males aged <12 years with severe haemophilia A (FVIII <1%) and >50 prior EDs with any FVIII product were eligible for the main study (age limit <6 years for the expansion study). Key exclusion criteria for the main study included presence or history of FVIII inhibitors (≥0.6 Bethesda units [BU]/mL), other bleeding disorders in addition to haemophilia A, platelet count <100,000/mm^3, creatinine more than twice the upper limit of normal (ULN), aspartate aminotransferase or alanine aminotransferase more than 5 times ULN, and known hypersensitivity to BAY 94-9027 or its components. Other exclusion criteria for the PROTECT VIII Kids main study are published elsewhere.[10]

2.2 | Study design

The design of the main study and the safety expansion study have been previously described.[10] PROTECT VIII Kids was a Phase 3, multicentre, open-label study. The main study was conducted from May 2013 to March 2015 and the expansion phase from October 2015 to August 2016,[10] with the extension phase running from March 2014 to February 2020. Eligible patients were enrolled in two age groups: <6 years and 6–<12 years.[10] In the main study, PTPs received BAY 94-9027 prophylaxis either twice weekly (25–60 IU/kg), every 5 days (45–60 IU/kg) or every 7 days (60 IU/kg). Dose and dosing interval could be changed at any time at physician discretion. The safety expansion study enrolled additional PTPs aged <6 years in order to obtain further safety data; these patients received BAY 94-9027 prophylaxis twice weekly (25–60 IU/kg) for 12 weeks.

Patients completing either the main study or the 12-week expansion study could continue in the optional extension phase. Dosing regimens in the extension study were the same as in the main and expansion studies; as before, patients could change dose and dosing interval at any time per investigator discretion and based on bleeding pattern.[10] Patients or their parents/guardians recorded bleeds and BAY 94-9027 treatment usage in an electronic diary and were followed for safety assessments every 6 months. Compliance with study treatment was calculated based on total number of infusions administered vs. calculated number of infusions per regimen.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. The study protocol received approval from each study site's Independent Ethics Committee or Institutional Review Board before the study start or amendment implementation, respectively. Written informed consent for the extension study was obtained from the parent/guardian before the study, and assent was also obtained, where appropriate.

2.3 | Efficacy assessments

The main efficacy variable in the extension phase was annualised bleeding rate (ABR) for total, joint, spontaneous and traumatic bleeds. ABR was additionally evaluated in the last 12 months of treatment. Treatment and response to treatment of bleeds and total FVIII consumption were also evaluated.

2.4 | Safety assessments

The main safety variable in the extension phase was frequency of inhibitor development. Inhibitor determination and other safety

variables were assessed at each 6-monthly study visit (±1 week) and at the final study visit; samples were obtained at trough levels of study drug. Laboratory testing was conducted for FVIII inhibitors (defined as a Nijmegen-modified Bethesda assay measured titre of ≥0.6 BU that was confirmed in a second independent sample, ideally collected within 2 weeks of the first inhibitor detection), anti-BAY 94-9027 antibodies (defined as anti-drug antibodies [ADA] that were specific for BAY 94-9027) and anti-PEG antibodies (defined as antibodies that were specific for the PEG moiety). For ADA determination, an enzyme-linked immunosorbent assay was used.

Additional parameters included in the assessment were height, weight and vital signs (including blood pressure, heart rate and body temperature). Quantitative plasma levels of free PEG were also measured using a combination of size-exclusion chromatography and tandem mass spectrometry detection with a lower limit of quantification (LLOQ) of 0.1 mg/L; bound PEG was not detected by this method. Following a protocol amendment, renal biomarker levels (albumin, beta-2 microglobulin, cystatin C, kidney injury molecule-1, lipocalin-2, proteinuria) were measured from month 18 in the extension until the study end in a variable number of patients; neurological assessments (based on neurological examinations performed by an investigator) were also conducted.

Patients were closely monitored for adverse events (AEs) throughout the study; data were collected on frequency of AEs, serious AEs (SAEs) and study drug–related AEs.

2.5 | Statistical analysis

Sample size was determined according to the requirements of the European Medicines Agency guidelines for clinical investigation of FVIII products. Total sample size was ≥25 patients for each age group at enrolment (<6 years or 6–<12 years). All analyses were based on patient age group at enrolment (<6 years or 6–<12 years) and/or treatment group at the start of the extension, with patients who changed their treatment regimen during the extension analysed in the 'variable dosing frequency' group. Subgroup analyses were performed for patients who completed ≥5 years of treatment during total time in the study.

Summary statistics were calculated for continuous data, and frequency tables were generated for categorical data. Exposure data are presented for the total time in the study (main study/expansion study, and the extension), as well as for the extension phase only. All other analyses refer to the extension period only.

3 | RESULTS

3.1 | Patients

A total of 73 PTPs were enrolled in the main or expansion studies, and 61 completed these studies. A total of 59/61 patients who completed the main/expansion studies (97%) continued to the extension phase (<6 years, n = 32; 6–<12 years, n = 27). Median age at enrolment was 5.0 years (3.5 years in patients <6 years; 9.0 years in patients 6–<12 years), and median age at the end of the extension was 12.0 years (9.0 years in patients <6 years; 15.0 years in patients 6–<12 years). Of 59 patients enrolled, 57 (97%) completed the extension study (52 completed ≥3 years of treatment during total time in the study; 41 completed ≥4 years; 39 completed ≥5 years). Two patients aged <6 years discontinued, due to a geographical relocation (n = 1) and cardiomyopathy related to a congenital disorder (n = 1; Figure 1). Demographic and clinical characteristics are shown in Table 1.

At the start of the extension, the majority of patients were treated every 5 days (n = 27), but at the end of the extension the majority were treated twice weekly (n = 29; Figure 2). Most patients (50/59; 85%) were on the same dosing frequency at the start and end of the extension phase; of these, 47 patients never varied their dosing frequency. Eight (13.6%) patients permanently increased frequency of dosing from every 5 days (n = 6) or every 7 days (n = 2) to a twice-weekly regimen during the extension study, and one patient (1.7%) decreased frequency of dosing from every 5 days to every 7 days.

Within both age groups, 58/59 patients (98.3%) accumulated ≥100 EDs during total time in the study, and one patient achieved 98 EDs. The median time (min; max) in the study (main and extension study combined) was 5.8 years (1.0; 6.6). Median time (min; max) in the extension phase only was 5.0 years (0.4; 5.9). During the entire study, patients accumulated a median (min; max) of 430.0 EDs (98; 671), with 378 EDs (42; 612) accumulated during the extension phase only. In the extension phase, the median total dose per infusion for all patients was 49.0 IU/kg, and the median total number of infusions per year was 77.5. Compliance with study treatment was >95% for all patients and all dosing regimens. The total median dose per year was 4062.4 IU/kg for all patients and 4160.1 IU/kg in patients who had completed ≥5 years of treatment (Table 2).

3.2 | Efficacy

For the 59 enrolled patients in the extension study, median total ABR was low (1.6), indicating effective bleeding control. Joint, spontaneous and traumatic ABRs were also low, at 0.8, 0.4 and 0.8, respectively. Median ABR was similar in both age groups across the different types of bleeds. Most bleeds were trauma-related. Total ABR was 1.5 in the <6 years of age group and 1.9 in the 6–<12 years of age group. For the <6 years of group versus the 6–<12 years of group, ABR for joint bleeds was 0.8 vs. 0.6, ABR for spontaneous bleeds was 0.4 vs. 0.3, and ABR for traumatic bleeds was 0.8 vs. 0.8, respectively. ABR for different bleed types across treatment regimens is shown in Figure 3A,B (also listed in Supplementary Table 1).

In the last 12 months of treatment, median total ABR was 1.0 (1.0 in the <6 years of group and 2.0 in the 6–<12 years of group) (Figure 3A,B). Median joint ABR was 1.0, and median spontaneous

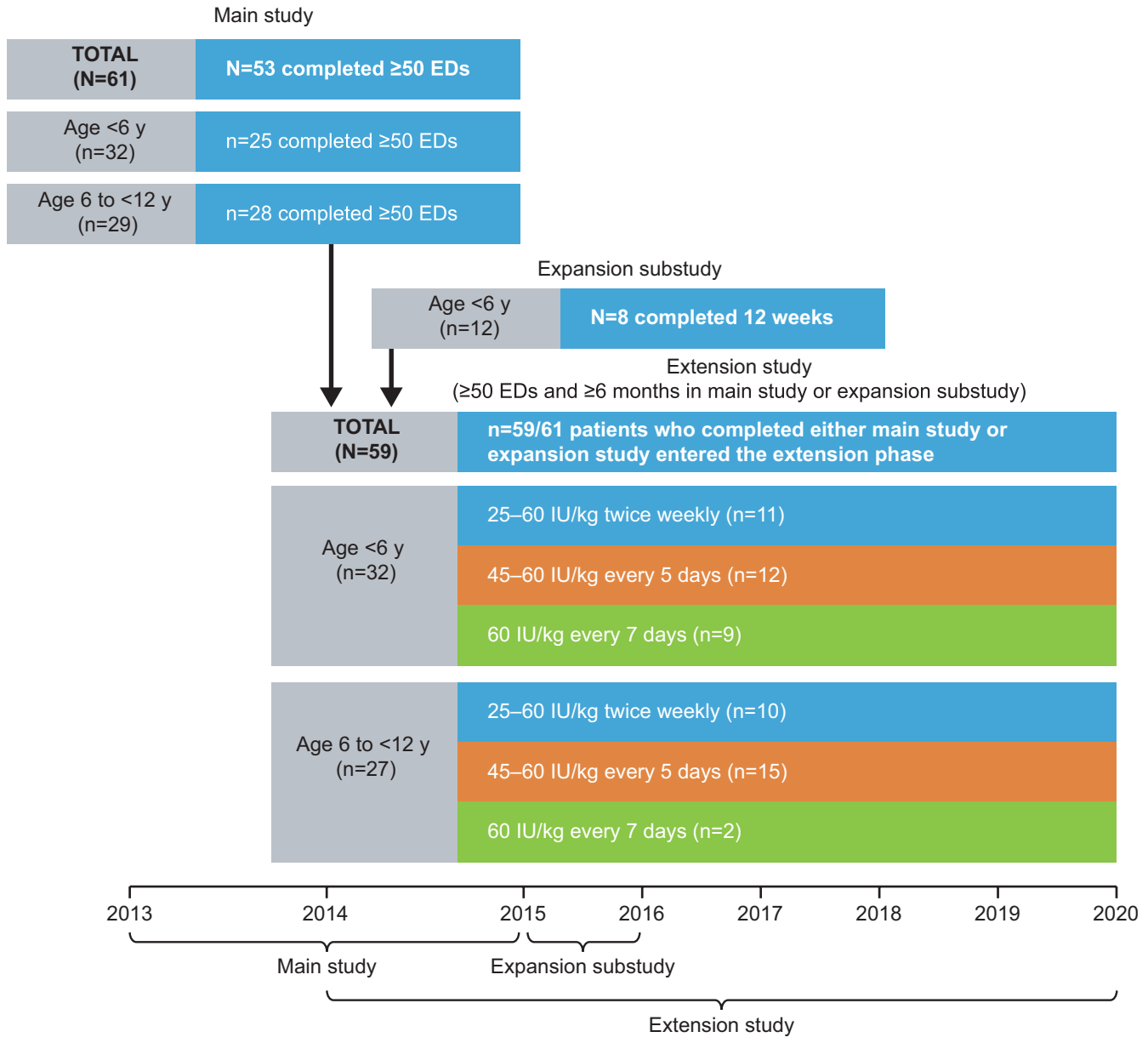


FIGURE 1 PROTECT VIII Kids study design. Regimens were based on treatment at beginning of the extension. ED, exposure day; y, years.

ABR was zero in both age groups. Traumatic ABR was higher in patients aged <6 years of group compared with the 6–<12 years of group (1.0 and 0.0, respectively). In total, 19 patients (33.3%) had zero bleeds, 27 patients (47.4%) had zero joint bleeds and 41 patients (71.9%) had zero spontaneous joint bleeds during the last 12 months in the extension study. Median ABR was also low for the subgroup of patients completing ≥5 years of treatment (Figure 4A,B).

Overall, 667 bleeds were reported during the extension study. The number of bleeds in age groups of <6 years and 6–<12 years was similar (323 bleeds and 344 bleeds, respectively). Regardless of age group and treatment regimen, most bleeds were mild (41.5%) or moderate (47.7%). The majority were related to trauma (500/667, 75%). Of 667 total bleeds, 319 (47.8%) occurred in joints; common sites included the ankle (29.2%), knee (26.6%) and elbow (16.9%) joints. Most bleeds required ≤2 infusions, and response to treatment was rated as good/excellent in the majority of cases (87.4%).

During the extension study, no major surgeries were performed, and 14 patients had 17 minor surgeries. Almost all surgeries (94%) were elective, with one emergency procedure to perform a tooth extraction. Where reported, haemostatic control was rated as 'good' or 'excellent' in all but one surgery, where it was rated as 'moderate'.

3.3 | Safety

Overall, 57 patients completed the extension phase. Two patients (both <6 years) discontinued, one due to an SAE (severe

TABLE 1 Demographics and baseline characteristics at enrolment.

Characteristic	All patients			Patients with ≥5 years of treatment		
	Aged <6 years (n = 32)	Aged 6–<12 years (n = 27)	Total (N = 59)	Aged <6 years (n = 17)	Aged 6–<12 years (n = 22)	Total N = 39)
Age at enrolment into main/expansion study, year						
Median (range)	3.5 (2–5)	9.0 (6–11)	5.0 (2–11)	3.0 (2–5)	9.0 (6–11)	6.0 (2–11)
Age at end of extension, year						
Median (range)	9.0 (3–12)	15.0 (10–18)	12.0 (3–18)	10.0 (8–12)	16.0 (13–18)	13.0 (8–18)
Race, n (%)						
White	26 (81.3)	26 (96.3)	52 (88.1)	15 (88.2)	21 (95.5)	36 (92.3)
Black	3 (9.4)	0	3 (5.1)	1 (5.9)	0	1 (2.6)
Asian	1 (3.1)	1 (3.7)	2 (3.4)	0	1 (4.5)	1 (2.6)
Other[a]	2 (6.2)	0	2 (3.4)	1 (5.9)	0	1 (2.6)
BMI[b], kg/m^2						
Median (range)	16.8 (13–27)	22.3 (16–31)	17.7 (13–31)	16.8 (15–27)	22.2 (16–31)	18.8 (15–31)
Previous treatment, n (%)						
Prophylaxis	31 (96.9)	23 (85.2)	54 (91.5)	16 (94.1)	20 (90.9)	36 (92.3)
On demand	1 (3.1)	4 (14.8)	5 (8.5)	1 (5.9)	2 (9.1)	3 (7.7)
Patients with target joints, n (%)	1 (3.1)	10 (37.0)	11 (18.6)	0	7 (31.8)	7 (17.9)
Bleeds in the previous 12 months[c], median (Q1; Q3)	2.5 (1.0; 9.0)	4.0 (2.0; 11.0)	3.0 (1.0; 10.0)	3.0 (1.0; 12.0)	4.0 (2.0; 9.0)	3.5 (1.5; 11.5)
Joint bleeds in the previous 12 months[c], median (Q1; Q3)	0.0 (0.0; 2.5)	2.0 (1.0; 5.0)	1.0 (0.0; 3.0)	0.0 (0.0; 3.0)	1.0 (1.0; 5.0)	1.0 (0.0; 3.0)

Abbreviations: BMI, body mass index; Q1, quartile 1; Q3, quartile 3.

[a]Other includes 'American Indian or Alaska native' and 'Native Hawaiian or other Pacific Islander'.

[b]At end of extension.

[c]Reporting period indicates previous 12 months before screening.

cardiomyopathy, related to a congenital disorder) and one due to 'other' factors (geographical relocation before study completion).

Overall, 56/59 patients (95%) had at least one AE during the extension period (Table 3). Most of the AEs were mild (12 events, 20.3%) or moderate (36 events, 61.0%), and eight events (13.6%) were severe. The frequency of AEs was similar in both age groups, with 31/32 patients (96.9%) aged <6 years and 25/27 patients (92.6%) aged 6–<12 years experiencing AEs. A total of 20 patients (33.9%) reported at least one SAE; a greater proportion of patients aged <6 years experienced SAEs compared with those aged 6–<12 years (13/32 [40.6%] vs. 7/27 [25.9%], respectively). No AE-related deaths were reported.

Study drug–related AEs were reported by four patients overall (6.8%). In the <6 years of age group, one patient had suspected FVIII inhibitors and one patient had severe muscle spasms. In the 6–<12 years of age group, two patients had suspected FVIII inhibitors (reported as drug-related SAEs per protocol requirement), with one of these patients also experiencing mild arthralgia. None of the three cases of suspected FVIII inhibitors were confirmed in a second sample (ie at a subsequent unscheduled visit, independent of 6-monthly study visits). Additionally, no AEs of special interest (AESI), defined as loss of efficacy or hypersensitivity reactions, were reported during the extension study. Clinical laboratory evaluations detected no abnormalities after ≥5 years of observation. No patients developed anti-BAY 94-9027 antibodies, and no anti-PEG antibodies were reported.

During the extension phase, 11/59 patients (18.6%) had detectable free PEG in plasma (n = 6 aged <6 years; n = 5 aged 6–<12 years). Free PEG was detected at a single time point for six patients and at repeated time points (≤4; one at the last visit) for five patients; the five patients with repeated positive results had all completed ≥5 years of treatment. Free PEG plasma levels remained just above the LLOQ (0.1 mg/L) in all cases (ranging from 0.100 to 0.152 mg/L) and did not increase over time in repeat-positive samples or decreased below the detection limit.

Levels of renal biomarkers (cystatin C, lipocalin 2, KIM-1, albumin, proteinuria, beta-2-microglobulin) were within normal ranges (where available; normal ranges have not been established in the paediatric population for all parameters assessed) and/or showed

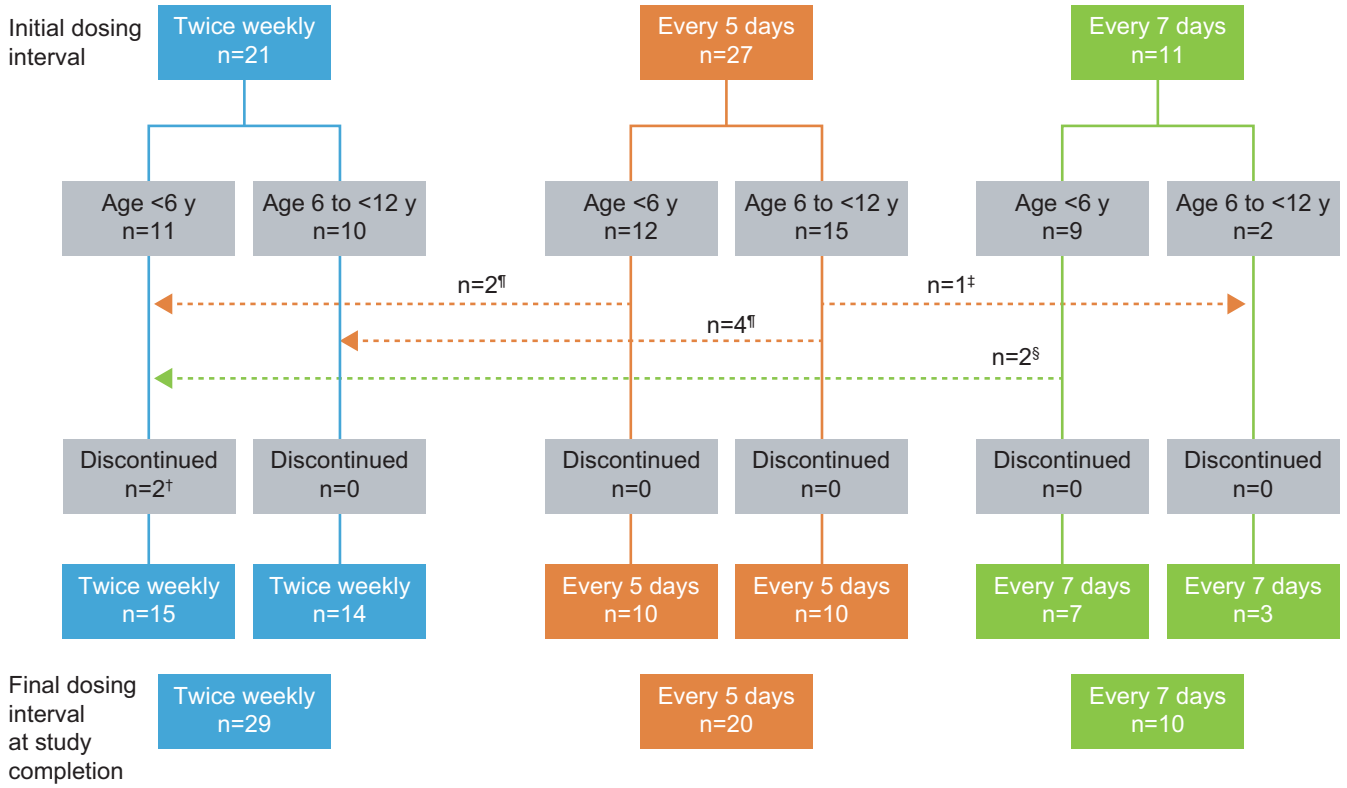


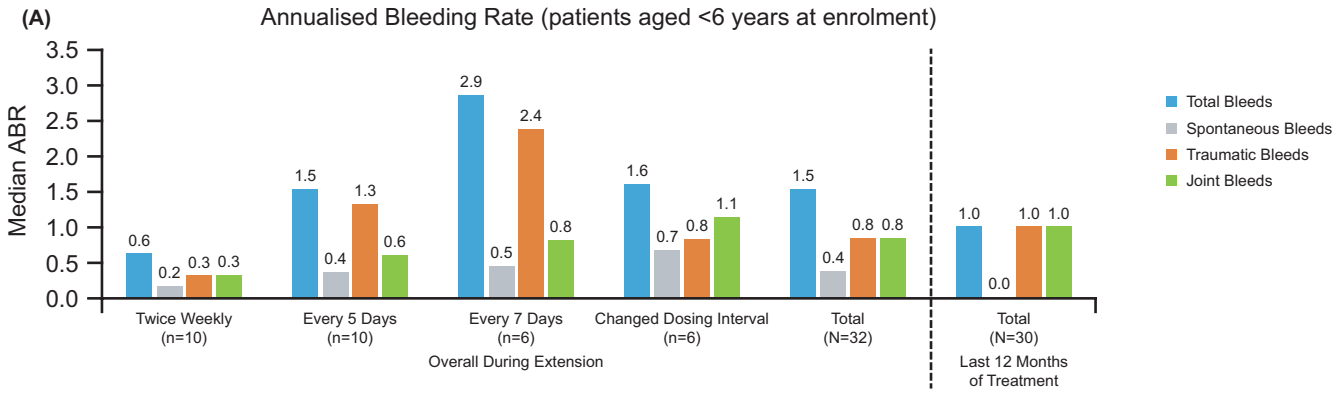
FIGURE 2 Patient disposition and treatment regimens during the PROTECT VIII Kids extension. †Discontinued due to adverse event (n = 1) or other (n = 1). ‡One patient aged 6 to <12 switched from every 5 days to every 7 days. §Two patients aged <6 years switched from every 7 days to twice weekly. ¶Two patients aged <6 years and 4 patients aged 6 to <12 years switched from every 5 days to twice weekly. y, years.

TABLE 2 BAY 94-9027 exposure during the PROTECT VIII Kids study.

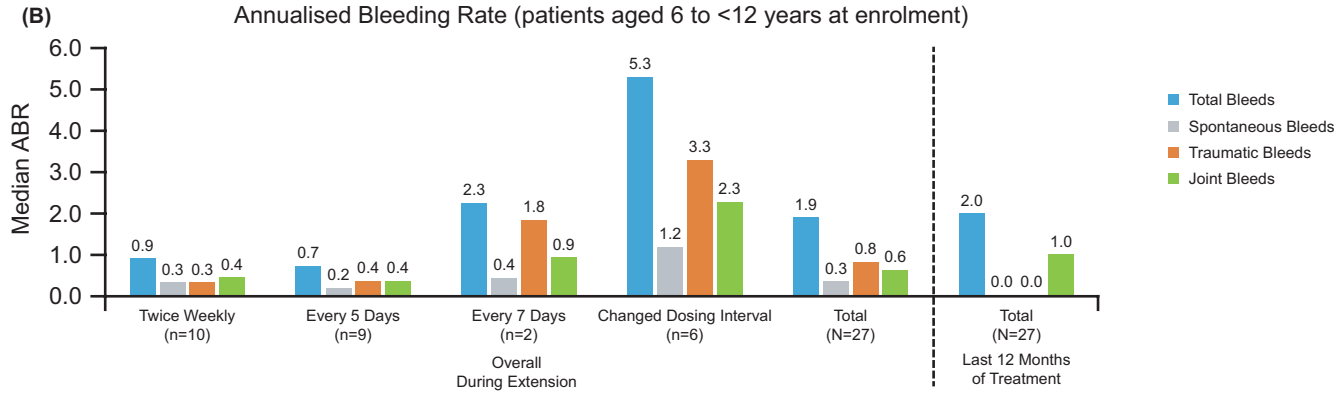
	All patients			Patients with ≥5 years of treatment		
Median (Q1; Q3); (range)	Aged <6 years (n = 32)	Aged 6–<12 years (n = 27)	Total (N = 59)	Aged <6 years (n = 17)	Aged 6–<12 years (n = 22)	Total (N = 39)
Time in study,[a] year	5.5 (3.5; 6.0); (1.0–6.4)	6.1 (5.3; 6.3); (2.5–6.6)	5.8 (3.9; 6.2); (1.0–6.6)	6.0 (5.7; 6.2); (5.5–6.4)	6.2 (6.0; 6.4); (5.2–6.6)	6.1 (5.8; 6.3); (5.2–6.6)
Time in extension, year	4.7 (3.1; 5.2); (0.4–5.7)	5.5 (4.7; 5.7); (2.0–5.9)	5.0 (3.5; 5.5); (0.4–5.9)	5.2 (5.0; 5.4); (4.5–5.7)	5.5 (5.3; 5.7); (4.5–5.9)	5.4 (5.0; 5.6); (4.5–5.9)
Exposure days in study[a]	390.0 (262.5; 468.0); (98–658)	477.0 (408.0; 529.0); (263–671)	430.0 (323.0; 511.0); (98–671)	465.0 (420.0; 602.0); (311–658)	482.5 (455.0; 558.0); (320–671)	477.0 (430.0; 602.0); (311–671)
Exposure days in extension	354.5 (220.5; 413.0); (42–597)	424.0 (355.0; 474.0); (210–612)	378.0 (270.0; 459.0); (42–612)	413.0 (369.0; 547.0); (260–597)	430 (397.0; 501.0); (269–612)	424.0 (374.0; 547.0); (260–612)
Dose per infusion in extension, IU/kg	54.7 (43.0; 58.4); (27–62)	45.0 (37.0; 56.9); (19–60)	49.1 (40.6; 57.2); (19–62)	54.5 (44.0; 58.7); (29–61)	49.4 (41.3; 57.1); (24–60)	53.4 (42.8; 57.6); (24–61)
Total dose in extension, IU/kg/year	4239.0 (3426.8; 4484.6); (2826–6879)	3942.1 (2962.8; 4313.7); (1992–4688)	4062.4 (3243.7; 4388.5); (1992–6879)	4355.1 (3462.2; 4486.4); (2979–5739)	4005.9 (3198.2; 4331.5); (2586–4688)	4160.1 (3342.1; 4438.7); (2586–5739)

Note: All data show median values unless otherwise specified.

[a]Includes main study, expansion study and extension phase.



	Overall During Extension					Last 12 Months of Treatment
	Twice Weekly	Every 5 Days	Every 7 Days	Changed Dosing Interval	Total	Total
Q1; Q3 for total bleeds ABR	0.0; 1.7	0.9; 3.5	0.8; 8.3	0.9; 2.9	0.7; 2.8	0.0; 3.0
Median (range) total dose per year, IU/kg	4222.0 (2747–6741)	4142.8 (3075–4490)	2999.8 (2876–3218)	4406.5 (2887–5617)	4076.8 (2747–6741)	Not reported



	Overall During Extension					Last 12 Months of Treatment
	Twice Weekly	Every 5 Days	Every 7 Days	Changed Dosing Interval	Total	Total
Q1; Q3 for total bleeds ABR	0.0; 2.8	0.4; 1.9	1.6; 2.9	3.1; 8.0	0.4; 3.3	0.0; 4.0
Median (range) total dose per year, IU/kg	3039.4 (1992–3942)	4148.4 (2815–4325)	2913.3 (2825–3002)	3960.6 (2928–4200)	3823.2 (1992–4325)	Not reported

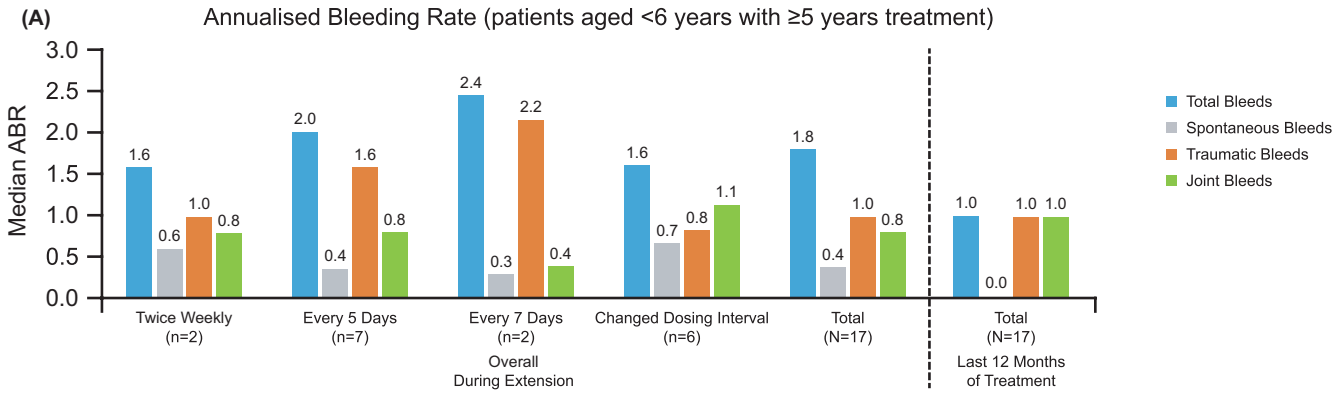
FIGURE 3 Summary of bleeds and BAY 94-9027 consumption by treatment regimen in all patients (A: aged <6 years; B: aged 6–<12 years) during the PROTECT VIII Kids extension. ABR, annualised bleeding rate; Q1, quartile 1; Q3, quartile 3.

no trend to increase, demonstrating normal renal function. Finally, no findings were reported from neurological examinations and no clinically relevant changes in vital signs (blood pressure, heart rate and body temperature) were detected.

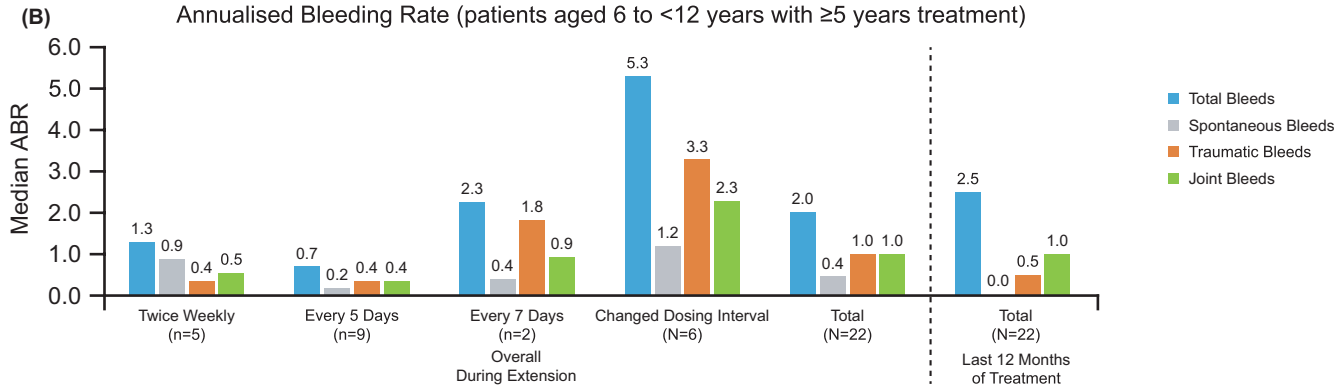
4 | DISCUSSION

BAY 94-9027 was efficacious and well-tolerated following ≥5 years of observation in paediatric patients with severe haemophilia A aged <12 years at enrolment. The safety profile of BAY 94-9027 in the extension phase was as expected for a FVIII product, and early signals of loss of efficacy or PEG-related hypersensitivity observed in the main study were not seen in the extension phase. The study drug continued to effectively prevent bleeding across both age groups, and all individually assigned treatment regimens.

Notably, total ABR improved numerically in comparison with the main study; this was maintained during the extension. The majority of bleeds were trauma-related and median ABR for joint and spontaneous bleeds was ≤0.8 in both age groups, with most bleeds reported as mild or moderate. BAY 94-9027 was also efficacious for the treatment of acute bleeds and provided haemostatic control during minor surgery. Most reported AEs were not related to BAY 94-9027. No new AESIs related to hypersensitivity or loss of efficacy were reported, and no anti-PEG antibodies, FVIII inhibitors or clinically relevant changes in renal biomarkers or vital signs were detected.



	Overall During Extension					Last 12 Months of Treatment
	Twice Weekly	Every 5 Days	Every 7 Days	Changed Dosing Interval	Total	Total
Q1; Q3 for total bleeds ABR	0.6; 2.6	0.8; 3.5	0.8; 4.1	0.9; 2.9	0.8; 2.9	1.0; 3.0
Median (range) total dose per year, IU/kg	3744.7 (3134–4355)	4457.2 (3166–4637)	3172.4 (2979–3366)	4486.6 (3462–5739)	4355.1 (2979–5739)	Not reported



	Overall During Extension					Last 12 Months of Treatment
	Twice Weekly	Every 5 Days	Every 7 Days	Changed Dosing Interval	Total	Total
Q1; Q3 for total bleeds ABR	0.5; 2.2	0.4; 1.9	1.6; 2.9	3.1; 8.0	0.5; 3.3	0.0; 4.0
Median (range) total dose per year, IU/kg	3939.0 (2586–4062)	4172.5 (2904–4389)	3080.5 (2963–3198)	4322.6 (3106–4688)	4005.9 (2586–4688)	Not reported

FIGURE 4 Summary of bleeds and BAY 94-9027 consumption by treatment regimen in the subgroup of patients (A: aged <6 years; B: aged 6–<12 years) who completed ≥5 years of treatment in the PROTECT VIII Kids extension. Based on all treatment administration during extension. ABR, annualised bleeding rate; Q1, quartile 1; Q3, quartile 3.

PEG is regarded as a non-immunogenic, non-antigenic moiety, but if an ADA binds to PEG, it is then viewed as an anti-PEG antibody. AESIs including hypersensitivity reactions have been previously associated with anti-PEG antibodies.[10] In the main study and its expansion, 12 patients (11 patients <6 years) discontinued BAY 94-9027 treatment due to perceived lack of efficacy and/or hypersensitivity reactions, which occurred within the first 4 EDs. Of these, four patients developed treatment-emergent anti-PEG IgM antibodies; this observed immune response (without any switch to IgG) was reported only in patients <6 years of age. In all cases, the IgM response did not persist after the patients resumed prior FVIII treatment.[10] This supports the theory that hypersensitivity reactions (such as early IgM response to PEG) are most likely to be observed during the first 4 EDs (ie during early exposure). For those patients who continued in the extension phase, no hypersensitivity, loss of efficacy or anti-PEG antibodies were detected, even in patients aged <6 years at main study entry.

As part of the safety analyses, free PEG in plasma was measured every 6 months throughout the extension phase up to 6 years of treatment. Free plasma PEG was not detected in the majority of patients following >5 years of observation in the extension phase. Eleven patients had detectable PEG, with five of these patients displaying presence of PEG at repeated time points. However, PEG levels in these five patients remained stable over the duration of the extension phase. These plasma PEG measurements are in line with predictions based on simulations of preclinical data.[11] No PEG-related safety concerns (ie PEG-related AEs, anti-PEG antibodies, neurological findings

TABLE 3 Treatment-emergent AEs during the PROTECT VIII Kids extension phase.

	All patients			Patients with ≥5 years of treatment		
Number of patients (%) with AE[a]	Aged <6 years (n = 32)	Aged 6–<12 years (n = 27)	Total (N = 59)	Aged <6 years (n = 17)	Aged 6–<12 years (n = 22)	Total (N = 39)
Any AE	31 (96.9)	25 (92.6)	56 (94.9)	17 (100.0)	20 (90.9)	37 (94.9)
Any study drug–related AE[b]	2 (6.3)	2 (7.4)	4 (6.8)	2 (11.8)	2 (9.1)	4 (10.3)
Maximum intensity for any AE						
Mild	7 (21.9)	5 (18.5)	12 (20.3)	1 (5.9)	1 (4.5)	2 (5.1)
Moderate	17 (53.1)	19 (70.4)	36 (61.0)	12 (70.6)	18 (81.8)	30 (76.9)
Severe	7 (21.9)	1 (3.7)	8 (13.6)	4 (23.5)	1 (4.5)	5 (12.8)
Maximum intensity for any study drug–related AE[b]						
Mild	1 (3.1)	1 (3.7)	2 (3.4)	1 (5.9)	1 (4.5)	2 (5.1)
Moderate	0	1 (3.7)	1 (1.7)	0	1 (4.5)	1 (2.6)
Severe	1 (3.1)	0	1 (1.7)	1 (5.9)	0	1 (2.6)
Any SAE	13 (40.6)	7 (25.9)	20 (33.9)	9 (52.9)	7 (31.8)	16 (41.0)
Any study drug–related SAE[b]	0	2 (7.4)	2 (3.4)[c]	0	2 (9.1)	2 (5.1)[c]
Discontinuation of study drug due to SAE	1 (3.1)	0	1 (1.7)	0	0	0
Deaths	0	0	0	0	0	0

Abbreviations: AE, adverse event; SAE, serious adverse event.

[a]All AEs were treatment-emergent, since patients entered the extension direct from the PROTECT VIII Kids main study or expansion substudy.

[b]As judged by the investigator.

[c]Both study drug–related SAEs were suspected (unconfirmed) factor VIII inhibitors.

[as performed by the investigator] or renal abnormalities) were reported in the extension. These long-term data confirm a good safety profile for BAY 94-9027, with no new safety findings or AESIs being observed in the paediatric patient population.

Treatment duration in the PROTECT VIII KIDS main and extension study is longer than that of other paediatric trials. By comparison, the Phase 3 Kids A-LONG trial and ASPIRE extension study, which evaluated a recombinant FVIII Fc fusion protein, had a median treatment duration of 3.5 years and 3.2 years, respectively, in paediatric subjects.[12,13] Additionally, the Phase 3 Pathfinder™ 5 main and extension study of glycoPEGylated recombinant FVIII turoctocog alfa pegol (N8-GP, ESPEROCT®) had a mean treatment duration of 4.5 years.[14,15] Finally, a Phase 3 study of PEGylated recombinant FVIII rurioctocog alfa pegol (BAX 855) was completed over a period of 6 months.[12,13,16] Overall, the safety and efficacy profile of BAY 94-9027 are similar to that reported in other recent paediatric trials,[13-15] with most reported bleeds being trauma-related.[14,16]

5 | CONCLUSION

Long-term (median 5.8 years) prophylactic treatment with BAY 94-9027 was efficacious and well-tolerated in both younger (<6 years) and older (6–<12 years) paediatric patients with severe haemophilia A at all dosing regimens, as well as during minor surgery. Results from the extension phase (median treatment duration 5.0 years) support the long-term safety of BAY 94-9027, with no PEG-related safety concerns and no anti-PEG antibodies reported. These findings showed that most children who started BAY 94-9027 prophylaxis when aged <12 years continued treatment into adolescence with sustained safety and efficacy.

ACKNOWLEDGEMENTS

The authors would like to acknowledge all clinical sites and investigators, the bioanalytical lab at Bayer and Yvonne Katterle, who was responsible for FVIII and NAB analyses. This study was supported by Bayer. Editorial support (in the form of writing assistance, including development of the initial draft based on author direction, assembling tables and figures, collating authors' comments, grammatical editing and referencing) was provided by Ewa Kilinska of Fishawack Communications Limited, part of Fishawack Health, and was funded by Bayer. PROTECT VIII Kids investigators are as follows: Argentina: M. Martínez; Austria: C. Male; Belgium: C. van Geet and V. Mondelaers; Bulgaria: V. Kaleva, A. Stoyanova-Deleva and D. Bobev; Canada: V. Blanchette and M. Steele; Greece: M-K. Economou; Israel: G. Kenet; Italy: E. Santagostino, E. Zanon and F. Gagliano; Lithuania: L. Rageliene; Netherlands: K. Fischer and M. Peters; New Zealand: M. Smith and J-A Bell; Norway: H. Glosli; Poland: W. Mlynarski and W. Badowska; Romania: M. Serban, L. Rusen and V. Uscatescu; Spain: R. Berrueco; United Kingdom: T. Biss, A. Will, J. Payne and O. Tunstall; United States: B. Kerlin, H. Yaish, R. Gruppo, S. Ahuja, M. E. Eyster, J. Ducore and J. Schwartz.

CONFLICT OF INTEREST

M.E.M. has acted as a paid consultant, advisor and/or speaker for Bayer, BioMarin, Catalyst, CSL Behring, Grifols, Kedrion, Novo Nordisk, Octapharma, PedNet Foundation, Pfizer, Roche, Sobi and Takeda. T.B. has received honoraria from Bayer and Boehringer Ingelheim. K.F. has acted as a consultant and/or speaker for Baxter/Shire, Bayer, Biogen, CSL Behring, Freeline, Novo Nordisk, Octapharma, Pfizer, Roche and Sobi. K.F. has also received research funding from Baxter/Shire, Bayer, Biogen, Novo Nordisk and Pfizer. M.M.E. is an employee of Bayer. M.S. has acted as a consultant and has received honoraria from Bayer. M.W. and D.T. are both employees of Bayer. S.A. has acted as a consultant for Genentech, Sanofi Genzyme and XaTek, Inc. S.A. has also received research funding, patents and royalties from XaTek, Inc, and has received honoraria from Genentech and Sanofi Genzyme. G.K. has acted as a consultant and/or speaker for Bayer, BioMarin, Novo Nordisk, Pfizer, Roche, Sanofi and Takeda, and has received research funding from Alnylam (Sanofi), Bayer, Pfizer, Roche and Shire. G.K. has also received honoraria from Bayer, BioMarin, CSL Behring, Novo Nordisk, Pfizer, PI Healthcare, Roche, Sanofi and Takeda, and has served on the board of directors or advisory committee for Bayer, BioMarin, Daiichi Sankyo, Novo Nordisk, Pfizer, Roche, Sanofi and Takeda.

AUTHOR CONTRIBUTIONS

M.E.M., T.B., K.F., M.S., S.A. and G.K. were principal investigators who treated patients and contributed to data acquisition and interpretation. M.M.E. was the sponsor's global clinical leader, responsible for the conduct of the study and contribution to data analysis and interpretation. M.W. contributed to data analysis and interpretation. D.T. was the clinical project manager, responsible for the conduct of the study and contribution to data analysis and interpretation. All authors contributed to the development of the manuscript and approved the final draft.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Bayer. Restrictions apply to the availability of these data, which were used under licence for this study. The 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, time point 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 01 January 2014. Interested researchers can use www.clinicalstudydatarequest.com 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 Study sponsors 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.

ORCID

Maria Elisa Mancuso https://orcid.org/0000-0002-7113-4028
Kathelijn Fischer https://orcid.org/0000-0001-7126-6613
Gili Kenet https://orcid.org/0000-0003-3494-9823

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SUPPORTING INFORMATION

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

How to cite this article: Mancuso ME, Biss T, Fischer K, et al. PROTECT VIII kids extension study: Long-term safety and efficacy of BAY 94-9027 (damoctocog alfa pegol) in children with severe haemophilia A. *Haemophilia*. 2021;27:434–444. https://doi.org/10.1111/hae.14294