ORIGINAL ARTICLE

Clinical haemophilia

PROTECT VIII Kids: BAY 94-9027 (PEGylated Recombinant Factor VIII) safety and efficacy in previously treated children with severe haemophilia A

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Abstract

Introduction: BAY 94-9027, a site-specifically PEGylated, B-domain–deleted recombinant factor VIII (FVIII) with extended half-life, demonstrated efficacy for bleed prevention and treatment in previously treated adolescents and adults with severe haemophilia A.

Aim: To assess BAY 94-9027 in children with severe haemophilia A.

Methods: In the two-part PROTECT VIII Kids study, boys <12 years with <1% FVIII and >50 exposure days (EDs) to FVIII were enrolled in two cohorts (<6 years; 6-<12 years) and treated with BAY 94-9027 prophylaxis twice-weekly, every 5 days, or every 7 days at physician discretion for ≥50 EDs (Part 1) or twice-weekly for 12-weeks (Part 2). Annualized bleeding rate (ABR) was a primary efficacy endpoint; FVIII inhibitor development was the primary safety variable.

Results: At study completion, 25 patients had been treated twice-weekly, 28 in the every-5-day group, and 8 in the every-7-day group. Median ABR for all bleeds was 2.9 (Part 1) and 2.4 (Part 2) and similar in younger and older patients; median ABR for joint bleeds was 0 for both cohorts. In the last 90 days' treatment, median ABR was 0 for younger and older patients (Part 1). Of 149 reported bleeds, 93% were treated with ≤2 infusions. Twelve patients, the majority <6 years (n = 11), discontinued due to apparent loss of efficacy or hypersensitivity. No FVIII inhibitors developed.

Conclusions: In PROTECT VIII Kids, which allowed tailoring of prophylaxis to individual clinical response, BAY 94-9027 was efficacious for bleed prevention and treatment in previously treated children with severe haemophilia A.

KEYWORDS
children, factor VIII, haemophilia A, polyethylene glycol, prophylaxis

1 | INTRODUCTION

Factor VIII (FVIII) replacement therapy is the standard of care for severe haemophilia A. FVIII products with extended half-lives offer the potential for less frequent infusions than standard-acting FVIII products and may decrease the burden of prophylaxis and improve adherence.[1,2] BAY 94-9027 (damactocog alfa pegol; Jivi®; Bayer[3]) is a B-domain–deleted recombinant FVIII (BDD-rFVIII) product that is site-specifically conjugated with a 60-kDa branched polyethylene glycol (PEG), resulting in one PEG per BDD-rFVIII protein. BAY 94-9027 has demonstrated an extended half-life (EHL) in children, compared with standard-acting FVIII products.[4,5]

In the phase 2/3 PROTECT VIII study, BAY 94-9027 demonstrated effective prophylaxis in adults and adolescents with severe haemophilia A with dosing up to every 7 days.[6] Assessing children as an independent population is necessary because of age-related differences in the pharmacokinetics of all FVIII products, which have a shorter half-life and faster clearance than in older patients.[4] BAY 94-9027 has a half-life of 19 hours in adults and adolescents,[6] which is reduced to 15-16 hours in children <12 years.[4] Similar reductions in half-life are seen for other EHL FVIII products in children compared with adolescents and adults, including rFVIIIFc (Elocta®; Sobi)[7] and glycoPEGylated turoctocog alfa (Espercot®; Novo Nordisk),[8] and benefits relating to prolonged half-lives, such as longer dosing intervals, may not be as profound in patients aged <12 years. Age-related differences in physical activity levels are also seen, with younger patients being generally more active than older patients; this difference needs to be considered when determining appropriate prophylaxis dosing.[9] Prevention of joint bleeding is particularly important in the paediatric population because of the relationship between joint bleeds and development of chronic arthropathy over time.[10]

The PROTECT VIII Kids study aimed to evaluate the efficacy and safety of BAY 94-9027 in previously treated children aged ≤12 years with severe haemophilia A.

2 | METHODS

2.1 | Patients

Boys <12 years with severe haemophilia A (FVIII <1%) and >50 prior exposure days (EDs) to any FVIII product were eligible. Key exclusion criteria included the presence or history of FVIII inhibitors (>0.6 Bethesda units [BU]/mL), any bleeding disorder other than haemophilia A, creatinine >2 times the upper limit of normal (ULN), aspartate aminotransferase or alanine aminotransferase >5 times ULN, platelet count <100 000/mm,[3] or known hypersensitivity to BAY 94-9027 or its components. Per guidelines for clinical investigation of FVIII products in children <12 years,[11] patients were enrolled across two age groups: <6 years and 6-<12 years.

2.2 | Study design

PROTECT VIII Kids was a phase 3, multicentre, open-label, single-arm study (NCT01775618), conducted from May 2013 to March 2015 in two parts.

In the main study (Part 1), patients were treated with BAY 94-9027 at one of three recommended dose intervals for ≥50 EDs and for a minimum of 6 months. Doses were extrapolated from experience in adolescents and adults in the phase 1 and phase 2/3 PROTECT VIII studies.[4,12] Patients received 25-60 IU/kg of BAY 94-9027 at least once per week; initial dosing recommendations were 25 IU/kg twice-weekly, 45 IU/kg every 5 days, or 60 IU/kg every 7 days. Investigators were encouraged to start with the least-frequent regimen that they believed was appropriate for the patient. Per protocol, the dose or dose frequency could be changed at any time, and dosage recommendations were provided if a patient experienced ≥2 breakthrough spontaneous muscle and/or joint bleeds within any 3-month period. Because the dose for every-7-day prophylaxis was not to exceed 60 IU/kg, patients in this group could only increase their dose frequency; patients treated twice-weekly could increase their dose, while those treated every 5 days could increase either their dose or dose frequency.

A 12-week substudy (Part 2) enrolled 12 additional children <6 years to obtain further safety data owing to a higher-than-expected withdrawal rate in this age group in Part 1. Patients in Part 2 received twice-weekly prophylaxis 25-60 IU/kg.

In Parts 1 and 2, BAY 94-9027 dosing for the treatment of breakthrough bleeds was determined based on bleed severity, patient's past experience with treatment of bleeds, and physician recommendations. Follow-up treatments were administered as needed.

Treatment data, bleeding episodes and response to treatment for breakthrough bleeds were recorded by the patient/parent or guardian in an electronic patient diary. The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice Guidelines. The study protocol received approval by each site's independent ethics committee/institutional review board before patient enrolment. Written informed consent was obtained from patients' legal guardians before study entry; if appropriate, assent was also obtained.

2.3 | Efficacy assessments

Primary efficacy variables in the main study (Part 1) included the annualized number of total bleeds during prophylactic treatment and assessment of response to treatment of bleeds. The annualized bleeding rate (ABR) for all bleeds (overall, joint, trauma and spontaneous) during prophylaxis was assessed in patients who achieved ≥50 EDs (study completers). ABR also was evaluated during the last 90 days of treatment to account for patients who changed prophylaxis dose or frequency during Part 1 of the study. The response to treatment of bleeds was evaluated by the patient or caregiver and was rated on a 4-point scale (excellent/good/moderate/poor).

Patients in Part 2 who completed the 12-week observation period were included in the efficacy evaluation of ABR.

2.4 | Safety assessments

In Part 1, the primary safety variable was development of FVIII inhibitors. Vital signs, physical examinations, laboratory safety, quantitative measurement of PEG and adverse events (AEs), including hypersensitivity and loss of efficacy, were also recorded. Hypersensitivity was defined as an allergic reaction and indicated by angioedema, burning and stinging at the infusion site, chills, flushing, generalized urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting or wheezing. Loss of efficacy was diagnosed clinically, based on the occurrence of unexpected bleeding events, absent or inadequate responses to treatment of a bleed, or abnormally low FVIII levels.

FVIII inhibitors were defined as antibodies specific for unmodified FVIII protein that inhibited FVIII activity. Development of FVIII inhibitors (≥0.6 BU/mL) was tested using a one-stage Nijmegen-modified Bethesda assay, as described previously,[12] on samples collected immediately before exposure to BAY 94-9027, after 10-15 EDs, after 50 EDs, and at any time inhibitor development was suspected.

Anti-drug antibodies were defined as antibodies directed against PEG that were specific for BAY 94-9027 and did not cross-react with unmodified FVIII. Patients were monitored for anti-BAY 94-9027 antibodies using an enzyme-linked immunosorbent assay at

baseline; months 1, 2 and 3; and at the final visit. If results were positive, further investigations were conducted to determine if the antibody was against PEG or FVIII and if the anti-PEG antibody subtype was immunoglobulin (Ig) M or IgE. Quantitation of free PEG in plasma was performed using a combination of size-exclusion chromatography and mass spectrometry at baseline and the final visit (the lower limit of quantification [LLOQ] was 0.1 mg/L).

In Part 2, the primary safety outcome was to characterize the potential immune response to BAY 94-9027 previously observed in Part 1, and to evaluate the type of antibodies against PEG. Patients in Part 2 completed weekly visits for physical examination and AEs. Testing for FVIII inhibitors was performed on samples collected at baseline and final visit; anti-BAY 94-9027 antibody testing was performed for samples collected at all visits except for Visit 9.

In Part 1 and 2, all laboratory analyses were performed by specialized central laboratories.

2.5 | Statistical analysis

Sample size (n ≥ 25 patients per age group) was determined according to the requirements set forth by the European Medicines Agency guidelines for investigations of FVIII products.[11] Statistical analyses were descriptive and performed using SAS software 9.1 or higher (SAS Institute Inc). Summary statistics were calculated for continuous data, and frequencies were calculated for categorical data. Subgroup analyses were performed to determine ABR for patients who increased their dose or changed dosing frequency and once a

TABLE 1 Demographics and baseline characteristics (safety population)

	Part 1			Part 2
	Aged < 6 y (n = 32)	Aged 6-<12 y (n = 29)	Total (N = 61)	Aged < 6 y (N = 12)
Age, y				
Median (range)	3.0 (2-5)	9.0 (6-11)	NA	4.0 (2-5)
Race, n (%)				
White	27 (84.4)	28 (96.6)	55 (90.2)	10 (83.3)
Black	3 (9.4)	0	3 (4.9)	0
Asian	1 (3.1)	1 (3.4)	2 (3.3)	1 (8.3)
American Indian or Alaska native	1 (3.1)	0	1 (1.6)	0
Native Hawaiian or other Pacific Islander	0	0	0	1 (8.3)
BMI, kg/m^2				
Median (range)	15.5 (13-18)	16.4 (13-22)	NA	15.3 (14-17)
Previous treatment, n (%)				
Prophylaxis	31 (96.9)	25 (86.2)	56 (91.8)	12 (100)
On demand	1 (3.1)	4 (13.8)	5 (8.2)	0
Patients with target joints, n (%)	1 (3.1)	10 (34.5)	11 (18.0)	0
Bleeds in the previous 12 mo, median (Q1; Q3)	1 (1.0; 5.0)	4.0 (2.0; 10.5)	3.0 (1.0; 9.0)	3.5 (0.5; 5.5)
Joint bleeds in the previous 12 mo, median (Q1; Q3)	0 (0; 1.0)	2.0 (0.5; 5.0)	1.0 (0; 3.0)	0 (0; 2.0)

Abbreviations: BMI, body mass index; mo, months; NA, not available; Q1, quartile 1; Q3, quartile 3; y, years.
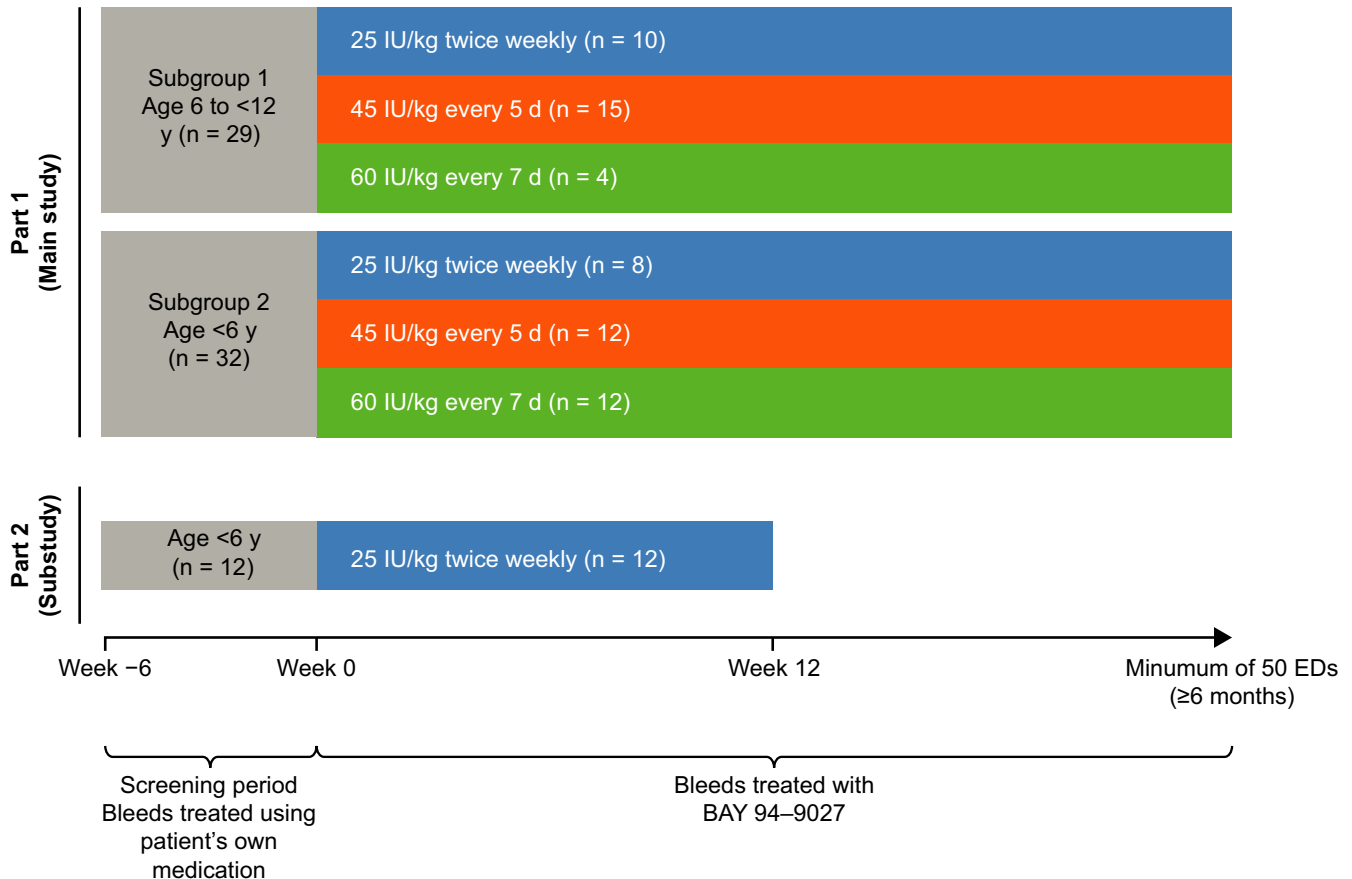
FIGURE 1 PROTECT VIII Kids study design. Part 1 starting dosing regimen of each patient was not randomized and selected by the investigator. Maximum age for subgroup 1 = 12 y minus 1 d when consent was signed; maximum age for subgroup 2 and Part 2 = 6 y minus 1 d when consent was signed. ED, exposure day; y, years

stable dose was achieved. All patients who received ≥1 dose of BAY 94-9027 were included in the safety analysis.

3 | RESULTS

A total of 61 patients from 31 centres in 13 countries received BAY 94-9027 in Part 1 (<6 years, n = 32; 6-<12 years, n = 29). Twelve patients from seven centres in six countries received BAY 94-9027 in Part 2. Demographic and clinical characteristics are shown in Table 1.

In Part 1, 18 patients were assigned by the investigator to twice-weekly dosing, 27 patients to every-5-day dosing, and 16 patients to every-7-day dosing (Figure 1). In the twice-weekly group, 3 patients discontinued, and the remaining patients maintained the same dosing frequency. In the every-5-day prophylaxis group, 4 patients discontinued and 1 patient reduced his dosing frequency to every 7 days. Eight patients in the every-7-day group switched to more-frequent dosing, and 1 patient discontinued after experiencing hypersensitivity with the first dose of BAY 94-9027 but was included in the safety analysis. At study completion, there were 17 patients in the twice-weekly group, 28 in the every-5-day group, and 8 patients in the every-7-day group for Part 1 (Figure 2). Overall, 53 of 61 treated

patients (87%) in Part 1 completed ≥50 EDs, and 44 (72%) remained on their initial dosing frequency. Eight patients completed Part 2, and 59 patients from Part 1 and Part 2 continued in the PROTECT VIII Kids extension study.[13]

Patients enrolled in Part 1 excluding the patient who discontinued after one ED had a mean ± standard deviation (SD; range) time in study of 233.6 ± 77.1 (15-448) days and accumulated a mean ± SD (range) of 50.0 ± 17.0 (3-68) EDs. Mean ± SD adherence across treatment groups was 99.6% ± 8.01% among the patients who completed ≥50 EDs during Part 1. Patients in Part 2 had a mean ± SD (range) time in the study of 65.7 ± 21.8 (31-86) days and accumulated a mean ± SD (range) of 18.1 ± 10.4 (3-30) EDs. The mean total dose in each treatment group is presented in Figure 3.

3.1 | Efficacy

In 53 patients who completed Part 1, the median (Q1; Q3) ABR for all bleeds was 2.9 (1.1; 6.1) and was similar in both age cohorts (Table 2 and Figure 3); median ABRs (Q1; Q3) for joint bleeds and spontaneous bleeds were 1.0 (0.0; 2.0) and 0.0 (0.0; 2.6), respectively. Twelve patients (22.6%) had 0 bleeds: four patients <6 years and eight patients 6-12 years.
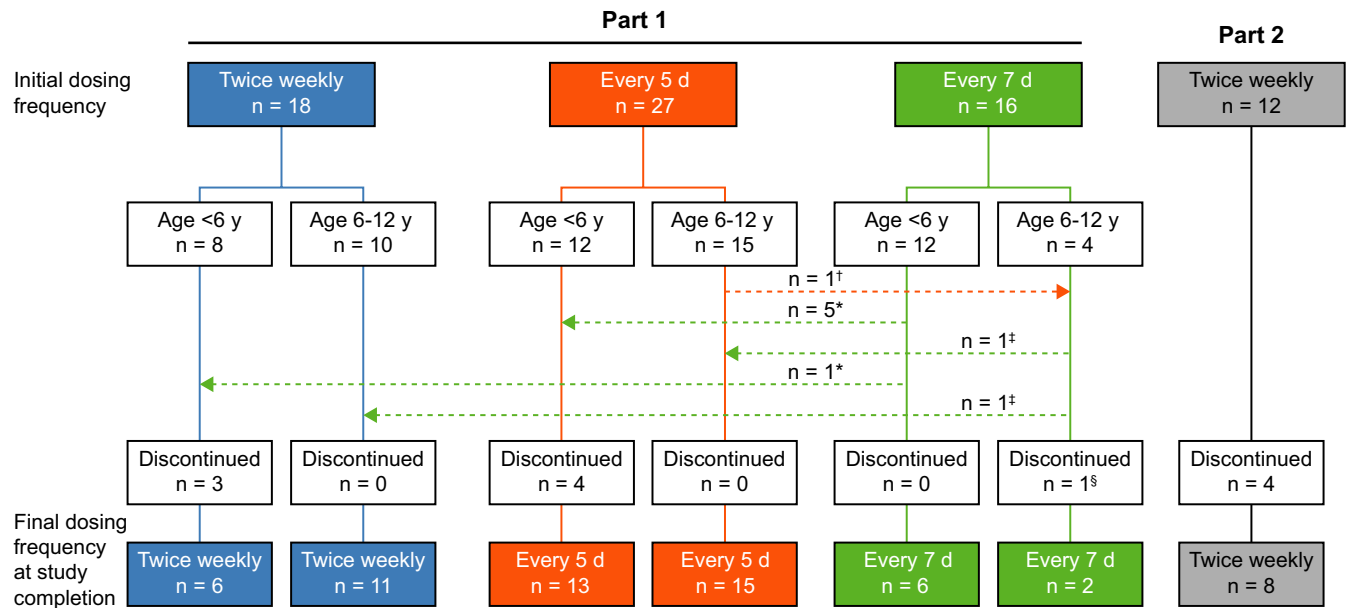
FIGURE 2 Patient disposition and treatment regimens during Part 1 and Part 2 PROTECT VIII Kids study. Arrows show movement of patients between regimens and do not reflect the time during the study when the switch occurred. *6 patients aged <6 y switched from every-7-d dosing to every-5-d dosing, one of these patients switched again from every-5-d dosing to twice-weekly regimen; †1 patient aged 6-<12 y switched from every-5-d dosing to every-7-d dosing; ‡1 patient aged 6-<12 y switched from every-7-d dosing to twice-weekly, and 1 patient in the same group switched from every-7-d to every-5-d dosing; §1 patient discontinued after receiving 1 dose of BAY 94-9027 and was not included in the efficacy evaluation, but was included in the safety population. y, years

Nine patients in Part 1 changed dosing frequency (Figure 2); for eight patients who switched from every-7-day dosing to more-frequent dosing, median ABR for all bleeds improved (Figure 4), and the median (Q1; Q3) number of all bleeds improved from 2.0 (1.0; 6.0) to 1.0 (0; 2.0). ABR for spontaneous, joint and trauma bleeds was also reduced after switching to more-frequent dosing. Median (Q1; Q3) ABR also improved in patients who increased their dose but did not change dosing frequency (twice-weekly arm [n = 6], 11.5 [2.2; 26.1] vs 1.4 [0; 10.0], before and after changing dose, respectively; every-5-day arm [n = 11], 11.1 [4.4; 19.2] vs 1.7 [0; 4.2]).

Comparison of ABR for all bleeds in the first 90 days vs the last 90 days of participants who completed Part 1 indicated that bleeding control markedly improved in both age cohorts as dosing regimens were adapted (Figure 5).

Of 140 bleeds reported during Part 1 of the study, 92% were controlled with one or two infusions of BAY 94-9027; response to treatment was rated by patients/caregivers as good or excellent for 85.7% of bleeds. Most bleeds were trauma related (n = 8, 63.0%), and most occurred in joints (n = 56, 40.0%), skin/mucosa (n = 41, 29.3%) or muscle (n = 26, 18.6%). Mean ± SD (range) dose to treat bleeds was 46.8 ± 11.3 (21-71) IU/kg per infusion.

In Part 2, eight patients completed the study and were included in the ABR evaluation. These patients had a total of nine bleeds (four traumatic, five spontaneous), corresponding to an ABR (Q1; Q3) of 2.4 (0-6.9; Table 2 and Figure 3); median ABRs (Q1; Q3) for joint bleeds and spontaneous bleeds were 0.0 (0.0; 2.4) and 0.0 (0.0; 2.2),

respectively. All bleeds were controlled with a single infusion of BAY 94-9027.

3.2 | Safety

In Part 1 of the study, BAY 94-9027 was well tolerated by the majority of patients for more than 50 EDs. There was no evidence of increased plasma-free PEG levels in Part 1; all PEG levels were below the LLOQ. No FVIII inhibitors were reported in Part 1 or Part 2.

Overall, 12 patients discontinued (eight from Part 1; four from Part 2); 11 were <6 years (Table S1). One patient discontinued due to the parent's decision and perceived lack of efficacy (Table S1) but no AEs were reported. All other discontinuations were related to perceived loss of efficacy and/or hypersensitivity reactions that occurred with the first four EDs; all AEs in patients who withdrew were transient, did not require intervention, and resolved when patients resumed treatment with their previous FVIII product. Of four patients who withdrew from Part 2 of the study, one tested positive for IgM anti-PEG antibodies at screening (Week −6-0) but not at baseline or during the study. Two patients tested positive for these antibodies at baseline and during the study, and one tested positive only during the study. No anti-PEG or anti-BAY 94-9027 antibodies were detected at the end of the study in patients who completed Part 2. One patient in Part 1 who had no pre-treatment anti-PEG antibody tested positive during treatment and at the final assessment (Table 3); these were short-lived anti-PEG IgM antibodies that disappeared when the patient resumed

(A)

■ All Bleeds ■ Spontaneous Bleeds ■ Joint Bleeds ■ Trauma Bleeds
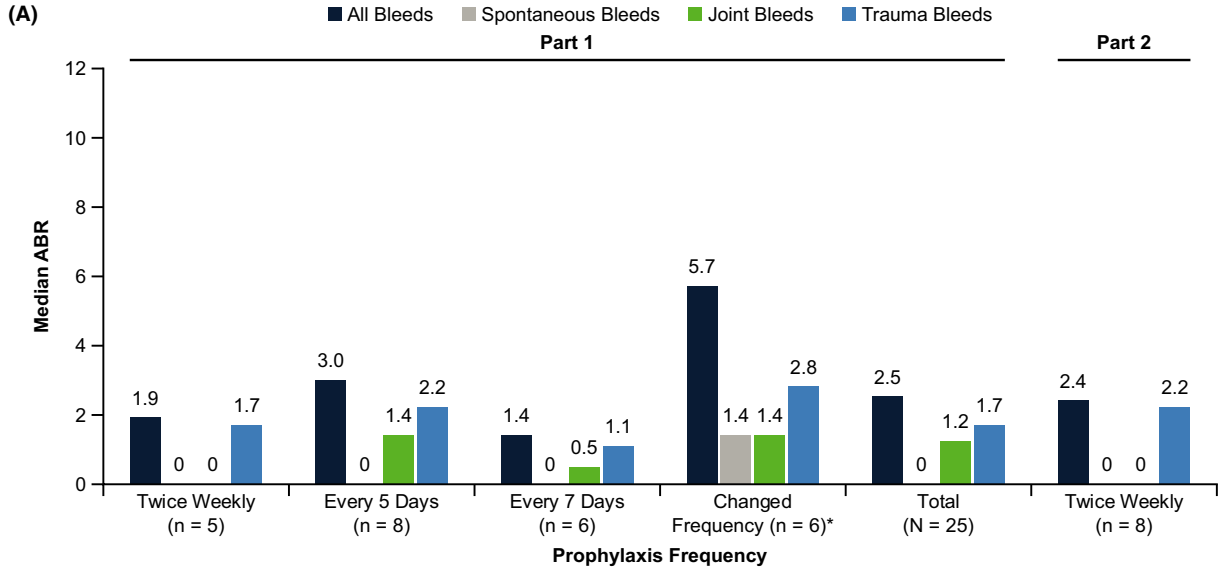
	Part 1					Part 2
	Twice Weekly	Every 5 Days	Every 7 Days	Changed Frequency	Total	Twice Weekly
Q1; Q3 for all bleeds	1.7; 2.0	1.3; 4.9	1.1; 4.8	2.5; 7.1	1.2; 5.2	0; 6.9
Median number of all bleeds (Q1; Q3)	1.0 (1.0; 1.0)	2.0 (1.0; 3.5)	1.5 (1.0; 5.0)	3.5 (2.0; 5.0)	2.0 (1.0; 4.0)	0.5 (0; 1.5)
Mean ± SD total dose in patients aged <6 y, IU/kg/y	4218 ± 1020 (n = 5)	4149 ± 513 (n = 8)	3189 ± 178 (n = 6)	4295 ± 437 (n = 6)	3967 ± 706 (N = 25)	4933 ± 931 (n = 8)

(B)
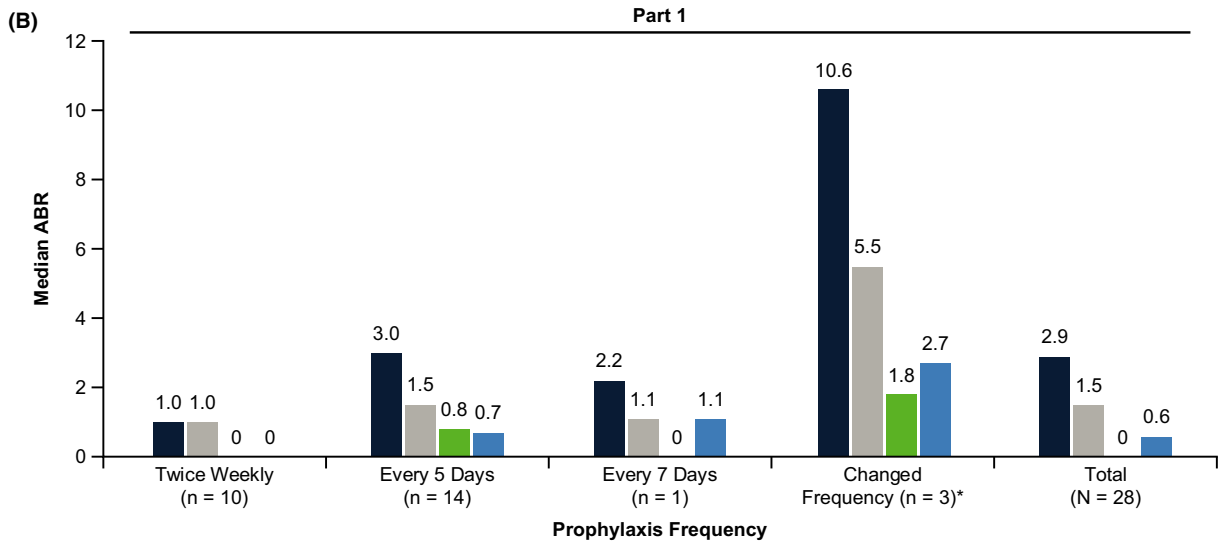
	Part 1				
	Twice Weekly	Every 5 Days	Every 7 Days	Changed Frequency	Total
Q1; Q3 for all bleeds	0; 5.6	1.4; 6.1	2.2	1.4; 11.0	0; 6.7
Median number of all bleeds (Q1; Q3)	0.5 (0; 3.0)	2.0 (1.0; 4.0)	2.0	6.0 (1.0; 8.0)	2.0 (0; 4.0)
Mean ± SD total dose in patients aged 6 to <12 y, IU/kg/y	3113 ± 697 (n = 10)	3715 ± 579 (n = 14)	3511 (n = 1)	3866 ± 616 (n = 3)	3509 ± 667 (N = 28)

FIGURE 3 Summary of bleeds and BAY 94-9027 consumption by regimen in all patients who completed Part 1 (n = 53) and Part 2 (n = 8) of the study. Panel A, patients aged <6 y; Panel B, patients aged 6-<12 y. *Patients who changed dosing frequency (increased or decreased). ABR, annualized bleeding rate; Q1, quartile 1; Q3, quartile 3; SD, standard deviation; y, years

TABLE 2 Summary of bleeds by age group and dosing frequency in Part 1 and Part 2 of the study (study completers)

| | Dosing Frequency Part 1 | | | | | Dosing Frequency Part 2 |
	Twice-weekly	Every 5 d	Every 7 d	Changed frequency[a]	Total	Twice-weekly
Patients aged <6 y, n	5	8	6	6	25	8
Number of all bleeds	1.0 (1.0; 1.0)	2.0 (1.0; 3.5)	1.5 (1.0; 5.0)	3.5 (2.0; 5.0)	2.0 (1.0; 4.0)	0.5 (0; 1.5)
ABR for all bleeds	1.9 (1.7; 2.0)	3.0 (1.3; 4.9)	1.4 (1.1; 4.8)	5.7 (2.5; 7.1)	2.5 (1.2; 5.2)	2.4 (0; 6.9)
ABR for spontaneous bleeds	0 (0; 0)	0 (0; 1.4)	0 (0; 0.8)	1.4 (0; 3.0)	0 (0; 1.3)	0 (0; 2.2)
ABR for joint bleeds	0 (0; 1.7)	1.36 (0; 1.5)	0.5 (0; 1.6)	1.4 (0; 2.5)	1.24 (0; 1.6)	0 (0; 2.4)
ABR for trauma bleeds	1.7 (0; 2.0)	2.2 (1.3; 3.5)	1.1 (0.8; 4.8)	2.8 (1.7; 4.3)	1.7 (1.1; 3.9)	2.2 (0; 4.6)
Patients with 0 bleeds, n (%)	1 (20.0)	1 (12.5)	1 (16.7)	1 (16.7)	4 (16.0)	4 (50.0)
Patients aged 6-<12 y, n	10	14	1	3	28	
Number of all bleeds	0.5 (0; 3.0)	2.0 (1.0; 4.0)	2.0	6.0 (1.0; 8.0)	2.0 (0; 4.0)	
ABR for all bleeds	1.0 (0; 5.6)	3.0 (1.4; 6.1)	2.2	10.6 (1.4; 11.0)	2.9 (0; 6.7)	
ABR for spontaneous bleeds	1.0 (0; 3.8)	1.5 (0; 2.8)	1.1	5.5 (0; 8.0)	1.5 (0; 3.0)	
ABR for joint bleeds	0 (0; 2.0)	0.8 (0; 2.9)	0	1.8 (0; 4.0)	0 (0; 2.8)	
ABR for trauma bleeds	0 (0; 1.9)	0.7 (0; 2.9)	1.1	2.7 (1.4; 5.5)	0.6 (0; 2.7)	
Patients with 0 bleeds, n (%)	5 (50.0)	3 (21.4)	0 (0)	0 (0)	8 (28.6)	

Note: Data are median (quartile 1; quartile 3) unless otherwise indicated.

Abbreviations: ABR, annualized bleeding rate; y, years.

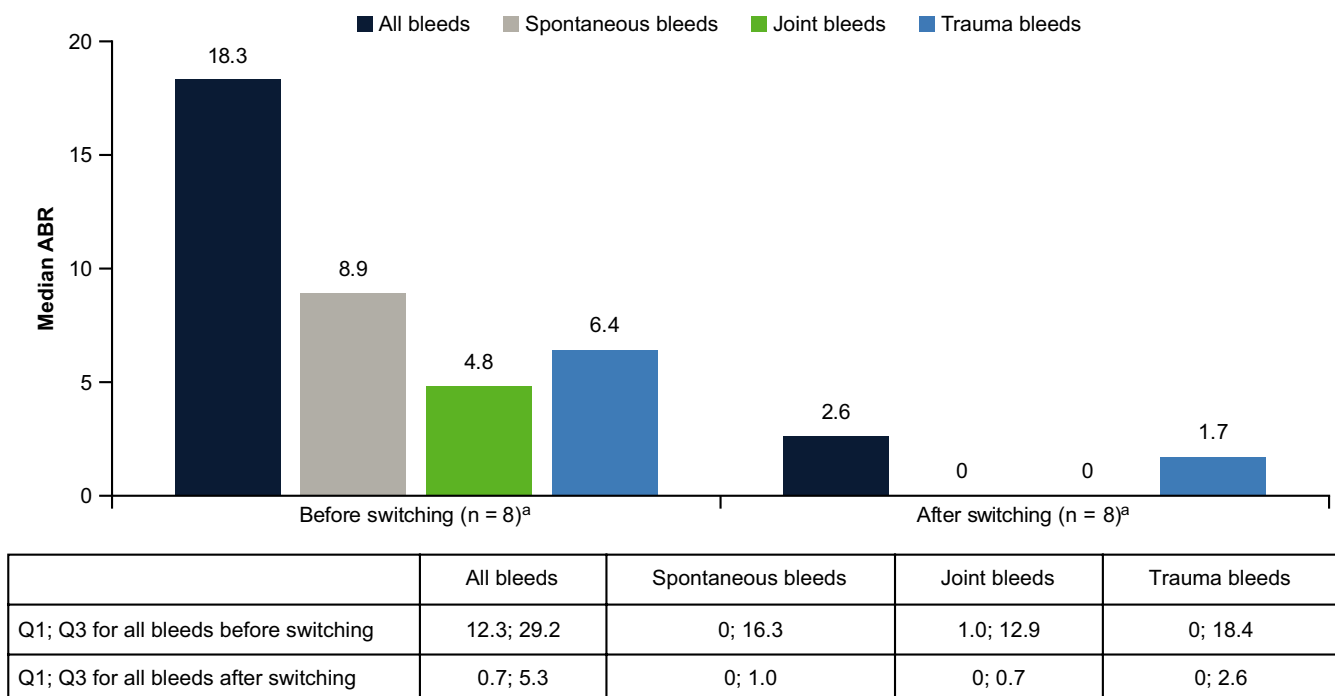[a]Patients who changed dosing frequency (increased or decreased).

	All bleeds	Spontaneous bleeds	Joint bleeds	Trauma bleeds
Q1; Q3 for all bleeds before switching	12.3; 29.2	0; 16.3	1.0; 12.9	0; 18.4
Q1; Q3 for all bleeds after switching	0.7; 5.3	0; 1.0	0; 0.7	0; 2.6

FIGURE 4 Annualized bleeding rates in patients who increased dosing frequency in Part 1 of the study. [a]8 patients increased dosing frequency from every 7 d to every 5 d (n = 6) or twice-weekly (n = 2). ABR, annualized bleeding rate; Q1, quartile 1; Q3, quartile 3

■ First 90 d   ■ Last 90 d

FIGURE 5   Summary of bleeds in the first and last 90 d for patients who completed Part 1 of the study. [a]Patients who changed dosing frequency (increased or decreased) during the indicated time period. ABR, annualized bleeding rate; N/A, not applicable; Q1, quartile 1; Q3, quartile 3; y, years
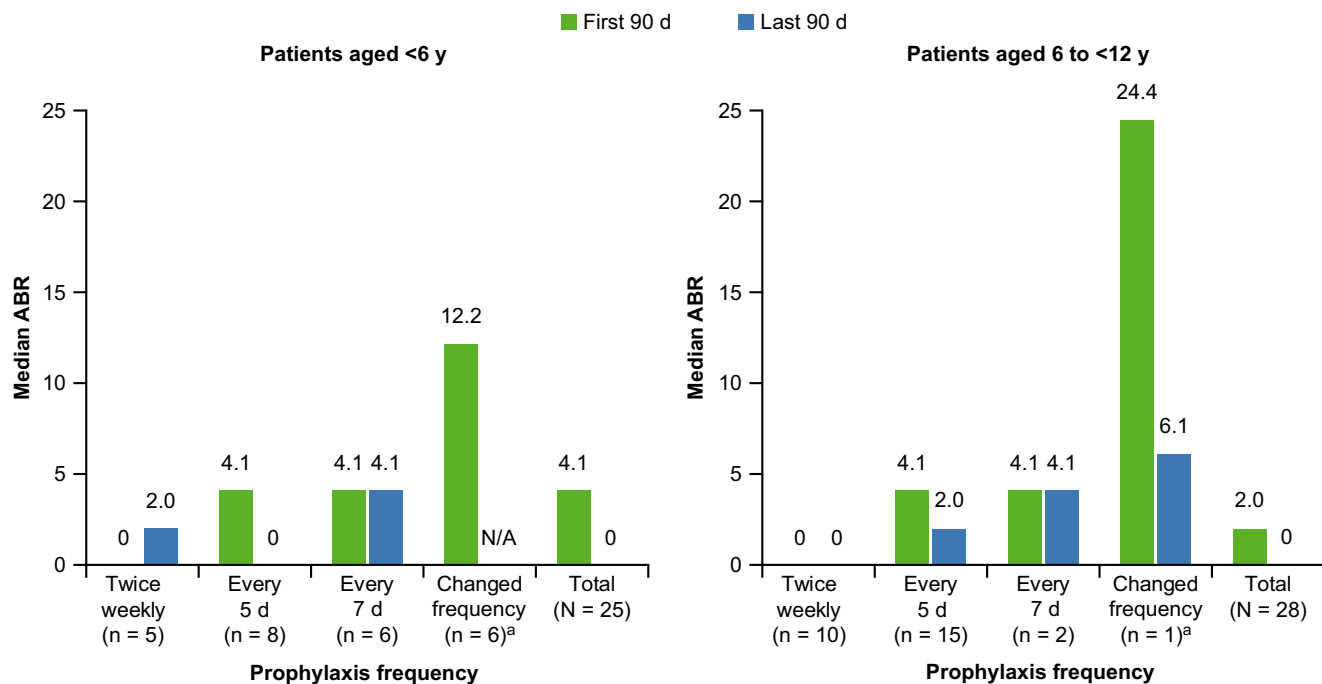
		Twice weekly	Every 5 d	Every 7 d	Changed frequency	Total
Patients aged <6 y	Q1; Q3 for all bleeds First 90 d of the study	0; 4.1	2.0; 4.1	0; 4.1	4.1; 12.2	0; 4.1
	Q1; Q3 for all bleeds Last 90 d of the study	0; 4.1	0; 4.1	0; 8.1	N/A	0; 4.1
Patients aged 6 to <12 y	Q1; Q3 for all bleeds First 90 d of the study	0; 8.1	0; 8.1	0; 8.1	N/A	0; 8.1
	Q1; Q3 for all bleeds Last 90 d of the study	0; 4.1	0; 4.1	N/A	0; 12.2	0; 4.1

their previous FVIII treatment. No anti-PEG IgE antibodies were detected in the patients who withdrew due to hypersensitivity reactions.

In Part 1, 50 of 61 patients (82%) who received BAY 94-9027 reported AEs (Table 4), the majority of which were of mild or moderate intensity. Nine patients (<6 years, n = 7; 6-<12 years, n = 2) experienced AEs that were assessed by the investigator as related to BAY 94-9027 (aged <6 years: moderate hypersensitivity, n = 2; spontaneous haemorrhage, n = 1; spontaneous haematoma, n = 1; subcutaneous haematoma, n = 1; contusion, n = 1; dysgeusia, n = 1. Aged 6-<12 years: moderate hypersensitivity, n = 1; epistaxis, n = 1). Six of these patients experienced serious AEs (moderate hypersensitivity, n = 2 aged <6 years and n = 1 aged 6-<12 years; anti-drug antibodies [not FVIII inhibitor], n = 3 aged <6 years).

In Part 2, 11 (92%) patients reported mild or moderate AEs, four of which were related to BAY 94-9027 (loss of efficacy; n = 3; hypersensitivity, n = 1) and two patients reported serious AEs (moderate hypersensitivity, n = 1; loss of efficacy, n = 1).

4 | DISCUSSION

BAY 94-9027 was efficacious for prophylaxis and treatment of bleeds in patients <12 years with severe haemophilia A, particularly when administered twice-weekly and every 5 days. No FVIII inhibitors were reported. Because the dosing regimens were at the discretion of the treating physician and were modified based on the needs of the individual patient, the study design reflects a real-world approach to prophylaxis; factors including level of physical activity and adherence[14-16] were taken into consideration when developing this dosing regimen. The open-label design and relatively short duration are potential limitations of this study, but are consistent with recent clinical studies in children for other EHL FVIII products.[17-19]

Most patients in Part 1 who completed the study remained at their initial dosing frequency. Of nine patients who switched, eight switched to a more-frequent dosing schedule; in all patients who switched, bleeding control was maintained or improved. Switching

TABLE 3 Combined results of antibody assays in Part 1 and Part 2 of the study (safety populations)

	Anti–BAY 94-9027	Anti-PEG	IgM Anti-PEG
	N = 73	N = 73	N = 73
Pre-treatment positive, n (%)	7 (9.6)	3 (4.1)	13 (17.8)
Negative during treatment	4 (57.1)	3 (100.0)	7 (53.8)
Positive during treatment[a]	3 (42.9)	–	6 (46.2)
Still positive at last measurement	1 (33.3)	–	3 (50.0)
Pre-treatment negative, n (%)	66 (90.4)	70 (95.9)	60 (82.2)
Missing during treatment	0	0	6 (10.0)
Negative during treatment	59 (89.4)	63 (90.0)	50 (83.3)
Treatment emergent positive	7 (10.6)	7 (10.0)	4 (6.7)
Still positive at last measurement	0	1 (14.3)	1 (25.0)

Abbreviation: PEG, polyethylene glycol.

[a]Any positive measurement during treatment.

TABLE 4 Patients with AEs considered treatment-related in Part 1 and 2 (safety populations)

	Part 1			Part 2	Combined
Number of patients (%) with AE	Aged < 6 y (n = 32)	Aged 6-<12 y (n = 29)	Total (N = 61)	Aged < 6 y (N = 12)	Part 1 and Part 2 (N = 73)
Any AE	29 (90.6)	21 (72.4)	50 (82.0)	11 (91.7)	61 (83.6)
Any study drug-related AE[a]	7 (21.9)	2 (6.9)	9 (14.8)	4 (33.3)	13 (17.8)
Maximum intensity for any AE					
Mild	13 (40.6)	13 (44.8)	26 (42.6)	7 (58.3)	33 (45.2)
Moderate	11 (34.4)	6 (20.7)	17 (27.9)	4 (33.3)	21 (28.8)
Severe	5 (15.6)	2 (6.9)	7 (11.5)	–	7 (9.6)
Any SAE	8 (25.0)	3 (10.3)	11 (18.0)	2 (16.7)	13 (17.8)
Any study drug-related SAE[a]	5 (15.6)	1 (3.4)	6 (9.8)	2 (16.7)	8 (11.0)
Discontinuation of study drug due to AE	6 (18.8)	1 (3.4)	7 (11.5)	4 (33.3)	11 (15.1)

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

[a]As judged by the investigator.

to a more-frequent dosing schedule was expected for two reasons. Firstly, investigators were encouraged to start their patients on the least-frequent infusion schedule appropriate for that patient, and a switch in dosing schedule was allowed at any time. Secondly, the half-lives of both standard half-life and EHL FVIII products are shorter in patients <12 years, compared with adolescents and adults, and so longer dosing intervals may not be as successful in children.[19-22] However, the ability of BAY 94-9027 to extend dosing frequencies beyond twice-weekly in paediatric patients was apparent: effective protection from bleeds was observed in the seven patients who remained on every-7-day prophylaxis (median ABR = 1.4 for six patients <6 years and 2.2 for the one patient 6-12 years), and every-5-day prophylaxis was the most frequently used regimen at the beginning and end of the study (45% and 53% of patients, respectively).

Eight (13.1%) patients in Part 1 (<6 years, n = 7) and four (33.3%) patients in Part 2 discontinued BAY 94-9027 because of perceived loss of efficacy/hypersensitivity, occurring within the first four EDs; the majority of these patients (11/12, 91.7%) were aged <6 years. All of these patients were able to safely resume their previous FVIII therapy. Anti-PEG antibodies were detected in some of these patients prior to BAY 94-9027 exposure, but also in patients who did not experience AEs or loss of efficacy. Antibodies to PEG were exclusively IgM with no evidence of class switching, and the immune response did not persist after patients resumed their previous FVIII treatment.

Lack of efficacy relating to formation of anti-drug antibodies has been observed with non-FVIII replacement therapies that do not contain PEG. In the HAVEN 2 trial (NCT02795767) investigating emicizumab in patients aged <12 years with haemophilia A and inhibitors,

one patient developed a clinically significant anti-drug antibody to emicizumab, resulting in loss of efficacy and eventual drug discontinuation.[23,24] Thus, all biological treatments including FVIII replacement and non-replacement therapy carry a certain risk of immunogenicity in paediatric patients and further investigation and caution are necessary.

The detection of anti-PEG antibodies, before and following exposure to PEGylated rFVIII, has been previously reported in children and adults. In the pathfinder 5 paediatric study, 31% of patients had anti-PEG antibodies before treatment with PEGylated turoctocog alfa (Espercot®; Novo Nordisk) and one patient developed anti-PEG antibodies after exposure; no impact of these antibodies on safety or efficacy of treatment was reported.[18] In the phase 3 trial of BAX 855 (Adynovate®; Baxalta US Inc) in children <12 years, five patients (7.6%) reported anti-PEG antibody (IgG) development during treatment,[25] while in the PROLONG-ATE study of BAX 855 in adolescents and adults with haemophilia A, three patients (2.2%) developed anti-PEG antibodies.[17] The occurrence of anti-PEG antibodies is not exclusive to haemophilia and rFVIII products. There are currently 20 PEGylated compounds approved for a variety of clinical indications.[26] The presence of antibodies to the PEG moiety has been associated with accelerated drug clearance resulting in loss of efficacy.[27,28] An extensive review of safety data for PEGylated therapies showed no specific association between particular AEs and PEG exposure over a period of decades.[26] No long-term PEG-related safety concerns have been reported in patients after chronic treatment with other PEGylated proteins, including nonacog beta pegol and certolizumab pegol.[29] Long-term exposure data with BAY 94-9027 over 5 years has been reassuring, and more long-term data will soon be available from the PROTECT VIII Kids extension study. Hypersensitivity reactions associated with other FVIII products are uncommon.[7,30]

Recently published preclinical investigations in rats have demonstrated that a mechanism for PEG excretion exists, even for higher molecular weight PEG molecules, such as the PEG-60 moiety in BAY 94-9027. Following degradation of the protein, free PEG is distributed, reaching a steady state in plasma after approximately 1 year; subsequently, no further increases in PEG in plasma are observed.[31,32] In PROTECT VIII Kids, no increases in free PEG were observed in the plasma of patients treated in Part 1. The long-term efficacy and safety of BAY 94-9027 are currently under investigation in children continuing treatment for >5 years; preliminary results suggest that there is no increase in plasma PEG levels over time (assessed every 6 months for up to 6 years) and no PEG-related safety concerns.[13]

5 | CONCLUSIONS

Using a study design that allowed tailoring of prophylaxis regimens to individualized patient response, BAY 94-9027 was effective for the prevention and treatment of bleeding episodes in previously treated patients aged <12 years with severe haemophilia. A total of 61 patients completed the study, with 59 continuing into the extension. For those patients who remained in the study, BAY 94-9027 was well tolerated and no FVIII inhibitors developed.

CONFLICT OF INTEREST

E. Santagostino has served on advisory boards/speakers bureau for Bayer, Bioverativ, CSL Behring, Grifols, Kedrion, Novo Nordisk, Octapharma, Pfizer, Roche, Shire/Takeda, Sobi, Spark and Uniqure. G. Kenet has received research grant support from Alnylam, Bayer, Bio Products Laboratory, Opko Biologics, Pfizer and Shire; has served as a consultant for and received honoraria from Alnylam, Bayer, Opko Biologics, Pfizer, Roche and Shire; and is a member of the advisory committee for Bayer, CSL Behring, Pfizer, Roche and Shire. K. Fischer has served on the speaker bureau for Bayer, Baxter, Biotest, CSL Behring, Novo Nordisk, Octapharma, Pfizer, and as an advisor for Bayer, Baxter, Biogen, CSL Behring, Freeline, Novo Nordisk, Pfizer, Roche and Sobi; and has received research support from Bayer, Pfizer, Baxter and Novo Nordisk. T. Biss has received research grant support from Leo Pharma, has served as a consultant for Bayer, and is a member of the speakers bureau for Bayer and Alexion. S. Ahuja has served as an advisory board member for Bayer, Shire, and Biogen and has served on speakers bureaus for Biogen, Novo Nordisk and Grifols. M. Steele has received honoraria from Bayer.

AUTHOR CONTRIBUTIONS

All authors were principal investigators who treated patients and contributed to data acquisition and interpretation. All authors contributed to the development of the manuscript and approved the final draft.

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SUPPORTING INFORMATION

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