PROTECT VIII Kids Trial Results: BAY 94-9027 Safety and Efficacy in Previously Treated Children With Severe Hemophilia A

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INTRODUCTION

- Prophylaxis reduces bleeding and improves joint outcomes vs on-demand treatment in patients with severe hemophilia A, especially when initiated at an early age.[1,2]
  - Early adoption of and adherence to prophylaxis may be facilitated by less frequent infusions using extended half-life factor VIII (FVIII) products.[3]
- BAY 94-9027 is a B-domain–deleted long-acting recombinant FVIII site-specifically conjugated with polyethylene glycol (PEG).[4]
  - BAY 94-9027 was demonstrated to have a prolonged half-life compared with unPEGylated recombinant FVIII in nonclinical studies and in adult patients with severe hemophilia A.[4,5]
- The safety and efficacy of BAY 94-9027 for prophylaxis and treatment of bleeds in adolescents and adults with severe hemophilia A was demonstrated in the PROTECT VIII trial.[6]
  - Efficacy of prophylaxis with BAY 94-9027 was shown at dose intervals up to every 7 days using a study design that allowed treatment to be tailored to individual patient responses.

OBJECTIVE

- The objective of this study was to evaluate the efficacy and safety of BAY 94-9027 for prophylaxis and treatment of bleeds in previously treated children with severe hemophilia A.

METHODS

Patients and Study Design

- This phase 3, multicenter, open-label, single treatment–arm study (PROTECT VIII Kids, ClinicalTrials.gov identifier: NCT01775618) was conducted at 31 centers in 13 countries from May 2013 to March 2015.
- Male patients aged <12 years with severe hemophilia A (FVIII <1%), >50 prior exposure days (EDs) to any FVIII product, and no inhibitors were treated with BAY 94-9027 for ≥50 EDs.
  - Patients were enrolled in 2 age groups (<6 years and 6–<12 years).
- BAY 94-9027 was started at 25 IU/kg twice weekly, 45 IU/kg every 5 days, or 60 IU/kg every 7 days; dose and dosing frequency were selected by the investigators, who were encouraged to start with the least-frequent infusion schedule that was appropriate for the individual patient.
  - The protocol encouraged increasing the dose or dosing frequency if a patient experienced 2 spontaneous muscle and/or joint bleeds within any 3-month period.

Assessments

- Primary efficacy endpoints were annualized number of bleeding events during prophylaxis and patient/parent assessment of response to treatment of bleeds on a 4-point scale (poor, moderate, good, excellent).
  - Further analysis was done in patients who increased their dose or changed dosing frequency to evaluate efficacy once a stable treatment regimen was achieved.
- Secondary endpoints included inhibitor development and safety.

RESULTS

Patients

- 61 patients were treated in the study **(Table 1)**, 60 of whom were included in the intent-to-treat population (aged <6 years, n=32; aged 6–<12 years, n=28); 8 patients discontinued treatment during the study.

Table 1. Demographics and Baseline Characteristics (Safety Population)

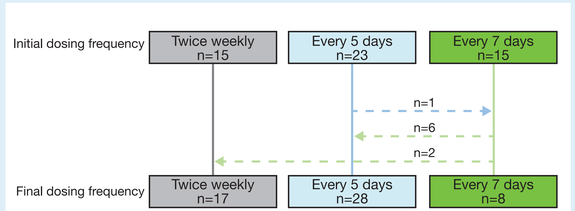
	Aged <6 y (n=32)	Aged 6–<12 y (n=29)	Total (N=61)
Age, y			
Median (range)	3.0 (2–5)	9.0 (6–11)	NA
Race, n (%)			
White	27 (84.4)	28 (96.6)	55 (90.2)
Black	3 (9.4)	0	3 (4.9)
Asian	1 (3.1)	1 (3.4)	2 (3.3)
American Indian or Alaska native	1 (3.1)	0	1 (1.6)
BMI, kg/m^2			
Median (range)	15.5 (13–18)	16.4 (13–22)	NA
Previous treatment, n (%)			
Prophylaxis	31 (96.9)	25 (86.2)	56 (91.8)
On demand	1 (3.1)	4 (13.8)	5 (8.2)
Patients with target joints, n (%)	1 (3.1)	10 (34.5)	11 (18.0)
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)
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)

BMI=body mass index; NA=not available; Q1=quartile 1; Q3=quartile 3.

Treatment

- All patients treated twice weekly or every 5 days remained at their assigned dose frequency with the exception of 1 patient who reduced his dosing frequency. Only patients treated every 7 days switched to more frequent dosing (8/15; **Figure 1**).

Figure 1. Treatment Regimens in Patients Who Completed the Study



Arrows show movement of patients between regimens and do not reflect the time during the study when the switch occurred.

- Mean ± SD dose per infusion for patients treated twice weekly, every 5 days, and every 7 days were as follows:
  - Patients aged <6 years: 35.3±6.3 (n=8), 51.4±5.8 (n=12), and 56.7±5.5 (n=6) IU/kg
  - Patients aged 6–<12 years: 29.0±5.9 (n=10), 47.6±5.7 (n=14), and 60.6 (n=1) IU/kg
- 33 of 51 patients (65%) who stayed at their initial dosing frequency did not change their dose, 17 (33%) increased their dose (every-5-days arm, n=11; twice-weekly arm, n=6), and 1 (2%) decreased his dose (twice-weekly arm). The study was designed to allow patients to find the appropriate and effective dose to tailor to their needs.

Efficacy

- For all 60 patients analyzed, median total ABR was similar in patients aged <6 and 6–<12 years **(Table 2)**; median ABRs for joint bleeds were 0 in both age groups and were low for spontaneous bleeds (0 and 1.5 for patients aged <6 and 6–<12 years, respectively).

Table 2. Summary of Bleeds by Age Group (Intent-to-Treat Population)

	Aged <6 y (n=32)	Aged 6–<12 y (n=28)	Total (N=60)
Number of bleeds			
Total	1.0 (1.0; 3.5)	2.0 (0; 4.0)	2.0 (0.5; 4.0)
Joint	0 (0; 1.0)	0 (0; 2.0)	0 (0; 1.0)
Spontaneous	0 (0; 1.0)	1.0 (0; 2.0)	0 (0; 1.0)
Trauma	1.0 (0; 2.0)	0.5 (0; 2.0)	1.0 (0; 2.0)
ABR			
Total	2.7 (1.1; 6.8)	2.9 (0; 6.7)	2.9 (0.5; 6.8)
Joint	0 (0; 1.6)	0 (0; 2.8)	0 (0; 1.9)
Spontaneous	0 (0; 1.6)	1.5 (0; 3.0)	0 (0; 2.8)
Trauma	1.6 (0; 4.1)	0.6 (0; 2.7)	1.4 (0; 3.1)
Patients with 0 bleeds, n (%)	7 (21.9)	8 (28.6)	15 (25.0)

ABR=annualized bleeding rate.
Data are median (quartile 1; quartile 3) unless otherwise indicated.

- Summary of bleeds by age group and dosing frequency is shown in **Table 3**.

Table 3. Summary of Bleeds by Age Group and Dosing Frequency

	Dosing Frequency			
	Twice Weekly	Every 5 Days	Every 7 Days	Changed Frequency*
Patients aged <6 y, n	8	12	6	6
Number of total bleeds	1.0 (0; 1.5)	1.0 (1.0; 2.5)	1.5 (1.0; 5.0)	3.5 (2.0; 5.0)
ABR for total bleeds	1.8 (0; 6.8)	3.9 (1.3; 20.0)	1.4 (1.1; 4.8)	5.7 (2.5; 7.1)
ABR for spontaneous bleeds	0 (0; 0.9)	0 (0; 2.2)	0 (0; 0.8)	1.4 (0; 3.0)
ABR for joint bleeds	0 (0; 1.8)	0 (0; 1.4)	0.5 (0; 1.6)	1.4 (0; 2.5)
Patients with 0 bleeds, n (%)	3 (37.5)	2 (16.7)	1 (16.7)	1 (16.7)
Patients aged 6–<12 y, n	10	14	1	3
Number of total bleeds	0.5 (0; 3.0)	2.0 (1.0; 4.0)	2.0	6.0 (1.0; 8.0)
ABR for total bleeds	1.0 (0; 5.6)	3.0 (1.4; 6.1)	2.2	10.6 (1.4; 11.0)
ABR for spontaneous bleeds	1.0 (0; 3.8)	1.5 (0; 2.8)	1.1	5.5 (0; 8.0)
ABR for joint bleeds	0 (0; 2.0)	0.8 (0; 2.9)	0	1.8 (0; 4.0)
Patients with 0 bleeds, n (%)	5 (50.0)	3 (21.4)	0 (0)	0 (0)

ABR=annualized bleeding rate.
Data are median (quartile 1; quartile 3) unless otherwise indicated.
*Patients who changed dosing frequency (increased or decreased); 8 patients switched from every-7-days dosing to every-5-days (n=6) or twice-weekly (n=2) dosing, and 1 patient decreased dosing frequency from every 5 days to every 7 days.

- A summary of total bleeds during the last 90 days of the study are shown for each dosing frequency in **Table 4**.

Table 4. Summary of Bleeds in the Last 90 Days of the Study*

	Dosing Frequency				
	Twice Weekly (n=17)	Every 5 Days (n=27)	Every 7 Days (n=7)	Changed Frequency (n=2)†	Total (n=53)
Number of total bleeds	0 (0; 1.0)	0 (0; 1.0)	1.0 (0; 2.0)	1.5 (0; 3.0)	0 (0; 1.0)
ABR for total bleeds	0 (0; 4.1)	0 (0; 4.1)	4.1 (0; 8.1)	6.1 (0; 12.2)	0 (0; 4.1)

Data are median (quartile 1; quartile 3).
*Data are for patients who completed the study.
†Patients who changed dosing frequency during the last 90 days of the study; 1 patient increased dosing frequency from every 7 days to every 5 days, and 1 patient decreased dosing frequency from every 5 days to every 7 days.

- 9 patients changed dosing frequencies (8 patients from every-7-days dosing) during the study after a mean (range) 107 (16–288) days. The mean (range) number of days in the study after the dosing frequency change was 152 (35–277) days.
  - For patients who switched from every-7-days treatment to more frequent dosing (n=8), median (Q1; Q3) number of total bleeds improved from 2.0 (1.0; 6.0) before switching to 1.0 (0; 2.0) after switching; median (Q1; Q3) ABR also improved from 18.3 (12.3; 29.2) before switching to 2.6 (0.7; 5.3) after switching **(Table 5)**.
  - For patients who remained in the every-7-days treatment arm throughout the study (n=7), the median (Q1; Q3) number of total bleeds was 2.0 (1.0; 5.0) and median (Q1; Q3) ABR was 1.6 (1.1; 4.8).

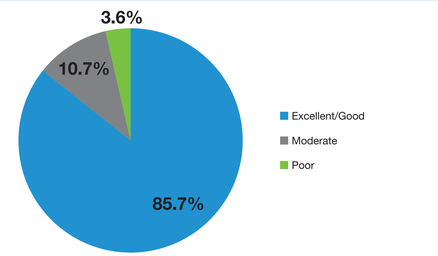
Table 5. ABR in Patients Who Increased Dosing Frequencies

ABR	Before Switching (n=8)*	After Switching (n=8)*
Total bleeds	18.3 (12.3; 29.2)	2.6 (0.7; 5.3)
Spontaneous bleeds	8.9 (0; 16.3)	0 (0; 1.0)
Traumatic bleeds	6.4 (0; 18.4)	1.7 (0; 2.6)
Joint bleeds	4.8 (1.0; 12.9)	0 (0; 0.7)

ABR=annualized bleeding rate.
Data are median (quartile 1; quartile 3).
*8 patients increased dosing frequency from every 7 days to every 5 days (n=6) or twice weekly (n=2).

- 129 of 140 bleeds (92%) reported during the study were controlled with 1–2 infusions.
- Response to treatment of bleeds was good or excellent in 85.7% of bleeds **(Figure 2)**; responses were similar in both age groups.

Figure 2. Patient/Parent Assessment of Response to Treatment of Bleeds (Intent-to-Treat Population)



Safety

- No inhibitors to FVIII were reported.
- 8 patients (aged 2–6 years) discontinued from the study because of suspected immunologic response against PEG, which occurred within 4 EDs to BAY 94-9027; no major safety concerns, including FVIII inhibitor development, were observed in these patients. All of these patients safely resumed their prior FVIII treatment at the same doses and frequencies as before the study.
  - The mechanism of these adverse events is being evaluated in a separate ongoing study.

CONCLUSIONS

- Every-5-days prophylaxis dosing was the most frequently used regimen at the beginning (45% of patients) and end (53% of patients) of the study.
- In a protocol allowing investigators to tailor prophylaxis treatment to individualized patient response, the long-acting product BAY 94-9027 was effective for prevention and treatment of bleeding in patients aged <12 years with severe hemophilia A once a stable dose regimen was obtained.
- No patient developed inhibitors to FVIII following administration of BAY 94-9027.

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Disclosures

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