Safety and efficacy of BAY 94-9027, a prolonged-half-life factor VIII

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To cite this article: Reding MT, Ng HJ, Poulsen LH, Eyster ME, Pabinger I, Shin H-J, Walsch R, Lederman M, Wang M, Hardtke M, Michaels LA. Safety and efficacy of BAY 94-9027, a prolonged-half-life factor VIII. J Thromb Haemost 2017; 15: 411–9.

Essentials

- Recombinant factor VIII BAY 94-9027 conjugates in a site-specific manner with polyethylene glycol.
- BAY 94-9027 was given to patients with severe hemophilia A as prophylaxis and to treat bleeds.
- BAY 94-9027 prevented bleeds at dose intervals up to every 7 days and effectively treated bleeds.
- BAY 94-9027 treatment was mainly well tolerated and no patient developed factor VIII inhibitors.

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Summary. Background: BAY 94-9027 is a B-domain-deleted prolonged-half-life recombinant factor VIII (FVIII) that conjugates in a site-specific manner with polyethylene glycol. Objective: Assess efficacy and safety of BAY 94-9027 for prophylaxis and treatment of bleeds in patients with severe hemophilia A. Patients/methods: In this multinational, phase 2/3, partially randomized, open-label trial, men aged 12–65 years with FVIII < 1% and ≥ 150 exposure days to FVIII received BAY 94-9027 for 36 weeks on demand or prophylactically at intervals determined following a 10-week run-in period on 25 IU kg⁻¹ body weight two times per week. Patients with > 1 bleed during the run-in subsequently received 30–40 IU kg⁻¹ two times per week; patients with ≤ 1 bleed were eligible for randomization to every-5-days (45–60 IU kg⁻¹) or every-7-days (60 IU kg⁻¹) prophylaxis (1 : 1) for 26 additional weeks until randomization arms were filled. Patients who were eligible but not randomized continued twice-weekly prophylaxis. The primary efficacy outcome was annualized bleeding rate (ABR). Results: The intent-to-treat population included 132 patients (prophylaxis, n = 112; on demand, n = 20). Median ABR (quartile [Q1; Q3]) for patients treated two times per week who were not eligible for randomization (n = 13) improved after dose increase (17.4 [14.3; 26.0] to 4.1 [2.0; 10.6]). Median ABR for patients randomized to every-5-days treatment (n = 43) was 1.9 (0; 4.2), similar to patients eligible for randomization but who continued treatment two times per week (n = 11). Median ABR for 32/43 patients (74%) who continued every-7-days prophylaxis until study end was 0.96 (0.0; 4.3). Six hundred and thirty-six of 702 bleeds (90.6%) were controlled with ≤ 2 infusions. No patient developed a FVIII inhibitor. Conclusions: BAY 94-9027 prevented bleeding across three individually tailored dose regimens and was effective for treatment of bleeds.

Keywords: clinical trial; factor VIII; hemophilia A; prophylaxis; recombinant proteins.

Introduction

In clinical studies, prophylaxis has been shown to reduce bleeding and improve joint outcomes compared with on-demand treatment in patients with severe hemophilia A [1,2]. As a result of such studies, the goal of therapy is to preserve normal musculoskeletal function [3,4]. Despite the benefits of prophylaxis, adherence to prophylaxis...
regimens is low [5], which may result in increased bleeding risk [6]. Barriers to prophylaxis include cost, lack of venous access, resistance to lifestyle changes, and perceived lack of benefit when symptoms are absent or infrequent [7]. Removal of these barriers is crucial for the improvement of clinical outcomes in patients with hemophilia A [7] because even a few joint bleeds can lead to irreversible arthropathy [1,8,9]. The success of prophylactic treatment may be improved by tailoring regimens to individual patients’ clinical needs and lifestyle [7]. Dosing regimens based on individual patient characteristics can provide effective bleed control [10–12]. Factor VIII (FVIII) products with prolonged half-lives may allow for less frequent dosing, which may further improve adherence to prophylaxis. The ability to tailor prophylaxis to the needs of each individual patient, including use of dosing intervals of up to 7 days with prolonged-half-life FVIII products, has the potential to improve clinical outcomes in patients with hemophilia A [7].

BAY 94-9027 is a B-domain-deleted recombinant FVIII (rFVIII) that conjugates in a site-specific manner to a single (dual-branched) 60-kD polyethylene glycol (PEG) molecule at an engineered cysteine [13]. The molecule was specifically engineered to prolong the activity of FVIII in circulation while retaining full coagulant activity with similar von Willebrand factor binding compared with unmodified rFVIII [13]. A phase 1 study in 14 patients with severe hemophilia A confirmed the approximately 50% longer half-life of BAY 94-9027 (~19 h) compared with sucrose-formulated rFVIII (~13 h), with comparable recovery [14]. In that study, all patients (n = 7) treated with 25 IU kg$^{-1}$ BAY 94-9027 twice weekly experienced 0 bleeding events over an 8-week treatment period. Pharmacokinetic (PK) modeling suggested that a dose of 45 IU kg$^{-1}$ every 5 days could achieve trough levels of > 1% in the majority of patients, and that a dose of 60 IU kg$^{-1}$ every 7 days would result in trough levels of > 1% in approximately 15% of patients [14].

Pharmacokinetic-based prophylaxis dosing is designed to maintain a predetermined FVIII trough level [15]; however, because the FVIII level is just one of several factors that influence bleeding phenotype, the appropriate FVIII trough level to prevent bleeding in each individual patient varies [16–18]. Thus, optimal prophylaxis dosing should take into account both PK and bleeding phenotype [18–20]. This principle was the basis for the design of the PROTECT VIII trial, a phase 2/3 study to assess the efficacy and safety of BAY 94-9027 in previously treated patients with severe hemophilia A. Based on the results of the phase 1 study, patients in PROTECT VIII were initially given doses of 25 IU kg$^{-1}$ BAY 94-9027 twice weekly [14]. Because previous studies with standard half-life products have shown that only approximately 20–30% of patients are protected from bleeds using 25 IU kg$^{-1}$ FVIII, even when given three times per week [21,22], it was anticipated that not all patients would have adequate bleed control when administered 25 IU kg$^{-1}$ BAY 94-9027 twice weekly. On the other hand, bleeding may be well controlled in some patients with less frequent dosing intervals, as predicted by PK modeling from the phase 1 study [14]. To distinguish between these two patient groups, observed bleeding during the initial 25 IU kg$^{-1}$ BAY 94-9027 twice-weekly treatment period (run-in period) was used to identify patients who would need more aggressive treatment compared with those who would likely benefit from less frequent infusions. The results of the PROTECT VIII study are reported here.

Methods

Patients

Part A of PROTECT VIII was conducted at 58 centers in 19 countries (Austria, Belgium, Canada, Colombia, Denmark, France, Germany, Israel, Italy, Japan, the Netherlands, Norway, Poland, Singapore, South Korea, Taiwan, Turkey, the UK and the USA). Men aged 12–65 years with severe hemophilia A (FVIII < 1%) previously treated with any FVIII product for ≥ 150 exposure days (EDs) were eligible. Key exclusion criteria included the presence or history of a FVIII inhibitor (≥ 0.6 BU mL$^{-1}$), diagnosis of any bleeding disorder other than hemophilia A, platelet count < 100 000/mm$^3$, creatinine > 2 times the upper limit of normal (ULN), or aspartate aminotransferase or alanine aminotransferase > 5 times the ULN. Part B of PROTECT VIII examined efficacy and safety during surgery; those results will be reported separately.

Study design

PROTECT VIII was a phase 2/3, multicenter, partially randomized, open-label, 36-week trial designed to assess the safety and efficacy of BAY 94-9027 for on-demand treatment and prophylaxis at various dosing frequencies in patients with severe hemophilia A (ClinicalTrials.gov identifier: NCT01580293). Patients receiving prophylactic therapy at the time of enrolment were only eligible for the prophylaxis arm of the study. Patients previously receiving on-demand therapy could choose to either receive BAY 94-9027 on demand for 36 weeks or enter the prophylaxis arm of the study. Patients in the prophylaxis arm were initially treated with twice-weekly 25 IU kg$^{-1}$ BAY 94-9027 during a 10-week run-in period, which was used to identify patients who had a more frequent bleeding tendency and thus were not expected to benefit from less frequent infusions (Fig. 1). Patients who experienced > 1 breakthrough bleed (defined as joint or muscle bleeds and no identified trauma) during the run-in period were considered to have high bleeding tendencies and were not eligible for randomization; these patients increased their dose to 30–40 IU kg$^{-1}$ to achieve higher FVIII levels and continued twice-weekly infusions for the remainder of the study. Patients with good bleed control (≤ 1 breakthrough bleed) during the run-in period were randomized 1 : 1 to receive
BAY 94-9027 every 5 days (starting at 45 IU kg⁻¹) or every 7 days (fixed dose of 60 IU kg⁻¹) for 26 weeks until these arms were full (capped at 43 patients). Patients eligible for randomization were assigned to treatment groups based on randomization generated by the sponsor’s randomization management system. A few patients (n = 11) with good bleed control (≤ 1 breakthrough bleed) during the run-in period, and who were thus eligible for randomization, continued with twice-weekly treatment for the remainder of the study after the randomization arms were filled. Patients in the every-5-days treatment arm could increase their dose up to 60 IU kg⁻¹ if the patient and investigator felt that bleed control was inadequate. After the dose increase, patients were allowed a one-time change to twice-weekly dosing if bleed control remained inadequate (adjustment was recommended in the case of ≥ 2 joint and/or muscle bleeds within any 10-week period). Patients in the every-7-days treatment arm were not allowed to increase their dose but were allowed a change to more frequent dosing (every 5 days or twice weekly) if bleed control was considered to be inadequate.

Bleeding events and administered infusions were recorded by patients using an electronic patient diary. The dose and number of infusions needed to treat bleeds was at the discretion of the investigator and patient. Written informed consent was provided by all patients or their legal guardians before entry into the study, and the study protocol was approved by each site’s independent ethics committee/institutional review board.

Safety assessments

Safety outcomes included the incidence and severity of adverse events (AEs) and serious AEs. Anti-FVIII inhibitor development (≥ 0.6 BU mL⁻¹) was monitored at baseline and weeks 2, 6, 10, 20 and 36 using the Nijmegen-modified Bethesda assay. The presence of binding anti-BAY 94-9027 antibodies against either PEG or FVIII was assessed at baseline and weeks 2, 6, 10, 20 and 36 by enzyme-linked immunosorbent assay; samples that were positive for anti-BAY 94-9027 antibodies were analyzed for possible neutralizing activity against BAY 94-9027.

Statistical analysis

Statistical analysis was performed using SAS software 9.2 (SAS Institute Inc., Cary, NC, USA). Summary statistics were calculated for continuous data, and frequencies were calculated for categorical data. The intent-to-treat (ITT) population (all patients who received ≥ 1 infusion of BAY 94-9027 for whom infusion and bleeding data were available) was used in the primary efficacy analysis. All patients who received ≥ 1 dose of study drug were included in the safety analysis. No formal statistics were performed to determine the sample size. The total size of the prophylaxis group (100–120 patients) was selected to ensure that ≥ 50 patients in the combined groups receiving treatment twice a week and every 5 days would accumulate ≥ 50 EDs.

Results

Study population

A total of 134 patients were treated in the study (Fig. 2). The mean age of all treated patients was 35.9 years; 13 patients (9.7%) were aged 12–17 years. The majority of patients were white (65.7%; Table 1). Overall, patients...
had a mean ± SD of 15.3 ± 18.6 bleeds in the previous 12 months (median, 8.5 [range 0–98] bleeds). Most patients (73.1%) had physician-reported target joint(s) at baseline; the number of target joints per patient (mean ± SD) was slightly higher in the on-demand group compared with patients in the combined prophylaxis group (2.5 ± 2.1 vs. 1.5 ± 1.5). Twenty patients comprised the on-demand group and the remaining 114 patients were in the prophylaxis group. Two patients on prophylaxis discontinued after a single dose (withdrawn consent, n = 1; adverse event, n = 1) and were not included in the ITT population (n = 132); however, these patients were included in the safety evaluation. Two additional patients withdrew from the prophylaxis group during the 10-week run-in period (withdrawn consent, n = 2). During the 10-week run-in period, 13 patients experienced > 1 breakthrough bleed and remained in the twice-weekly group for the remainder of the study (hereafter referred to as the twice-weekly not eligible for randomization group). The other 97 patients (88%) on prophylaxis experienced ≤ 1 breakthrough bleed during the run-in period on twice-weekly treatment; of these, 86 patients were randomized 1 : 1 to prophylaxis every 5 days (n = 43) or every 7 days (n = 43). The remaining 11 patients were not randomized because the treatment groups with less frequent dosing intervals were full; these patients continued with twice-weekly prophylaxis (hereafter referred to as the twice-weekly eligible but not randomized group). Eleven patients (25.6%) in the every-7-days group experienced ≥ 1 bleed (median, 2.0 [range, 1–6] bleeds) and their dosing frequency was increased to every 5 days (n = 8) or twice weekly (n = 3). These patients were considered a failure of treatment, remained in the study for safety assessment and underwent a separate efficacy analysis after changing dosing frequency. No patients in the every-5-days treatment group increased their dosing frequency.

The mean ± SD study duration was 246.7 ± 41.3 days. Patients accumulated a mean ± SD (range) of 55.3 ± 19.0 (1–99) EDs; 93 patients (69.4%) accumulated ≥ 50 EDs.

**Efficacy**

**Treatment of bleeds (weeks 0–36)**  A total of 702 bleeding events occurred during the study in both the on-demand and prophylaxis treatment groups. The
Table 1 Patient demographics and baseline clinical characteristics (safety population)

| Characteristic | On demand | Two times per week withdraw* | Two times per week not eligible for randomization | Two times per week eligible but not randomized† | Every 5 days | Every 7 days | All patients (N = 134) |
|----------------|-----------|------------------------------|-----------------------------------------------|-----------------------------------------------|--------------|--------------|--------------------------|
| Age            | 44.8 ± 13.5 | 27.3 ± 14.2                  | 31.4 ± 11.6                                   | 33.1 ± 11.0                                   | 33.7 ± 13.0  | 37.0 ± 13.5  | 35.9 ± 13.5               |
| Race, n (%)    | 11 (55.0)   | 4 (100)                      | 6 (46.2)                                      | 10 (90.9)                                     | 29 (67.4)    | 28 (65.1)    | 88 (65.7)                 |
| White          | 1 (5.0)     | 0                            | 0                                             | 1 (2.3)                                       | 3 (7.0)      | 5 (3.7)      |                           |
| Black          | 5 (25.0)    | 0                            | 7 (53.8)                                      | 1 (9.1)                                       | 11 (25.6)    | 8 (18.6)     | 32 (23.9)                 |
| Asian          | 3 (15.0)    | 0                            | 0                                             | 2 (4.7)                                       | 4 (9.3)      | 9 (6.7)      |                           |
| BMI, kg m⁻²    | 24.4 ± 4.3  | 22.7 ± 5.5                   | 23.5 ± 3.9                                    | 23.2 ± 3.9                                    | 24.8 ± 5.1   | 25.6 ± 4.7   | 24.7 ± 4.7               |
| Patients with target joints, n (%) | 16 (80.0) | 2 (50.0)                      | 11 (84.6)                                     | 10 (90.9)                                     | 28 (65.1)    | 31 (72.1)    | 98 (73.1)                 |
| Number of target joints per patient, mean ± SD | 2.5 ± 2.1 | 0.8 ± 1.0                     | 1.5 ± 1.0                                     | 2.3 ± 1.7                                     | 1.3 ± 1.5    | 1.7 ± 1.5    | 1.7 ± 1.6                 |
| Gilbert score, mean ± SD | 26.8 ± 11.8 | 16.5 ± 20.7                  | 20.3 ± 10.7                                   | 27.3 ± 21.0                                   | 18.0 ± 11.2  | 21.4 ± 13.5  | 21.3 ± 13.5               |
| Total          | 16.5 ± 7.8  | 11.0 ± 12.6                  | 11.7 ± 7.7                                    | 18.1 ± 12.9                                   | 12.4 ± 9.0   | 15.2 ± 10.3  | 14.2 ± 9.7                |
| Joint          | 27.9 ± 17.8 | 11.8 ± 16.1                  | 21.1 ± 17.8                                   | 28.7 ± 32.4                                   | 11.4 ± 15.7  | 8.1 ± 11.8   | 15.3 ± 18.6               |
| Number of bleeds in previous 12 months, mean ± SD | 3 (15.0) | NA                           | NA                                           | NA                                           | NA           | NA           | 9 (6.7)                   |
| HIV infection, n (%) | 9 (45.0) | NA                           | NA                                           | NA                                           | NA           | NA           | 40 (29.9)                 |
| HCV infection, n (%) | 3 (15.0) | NA                           | NA                                           | NA                                           | NA           | NA           | 9 (6.7)                   |

BMI, body mass index; HCV, hepatitis C virus; NA, not available. *Patients discontinued during the 10-week run-in period. †Not randomized because every-5-days and every-7-days randomization arms were full. ‡Includes six patients from the overall prophylaxis population. §Includes 31 patients from the overall prophylaxis population.

mean ± SD (range) dose to treat bleeds was 33.7 ± 10.4 (14-62) IU kg⁻¹ per infusion and most bleeds (90.6%) were treated with ≤ 2 infusions (Fig. 3). The mean length of time to treat bleeds between the first and second infusion was 2.1 days. The majority of patients (72.4%) reported good or excellent response to the treatment of bleeds.

Run-in period of twice-weekly prophylaxis (weeks 0–10)

The median (Q1; Q3) numbers of spontaneous joint or muscle bleeds with no identified trauma in the first 10 weeks of the study for patients ultimately randomized to the every-5-days and every 7-days treatment groups were 0 [0.0] and 0 [0.0], respectively. Patients in the twice-weekly eligible but not randomized group had a similarly low median (Q1; Q3) number of bleeds in the first 10 weeks (0 [0.0]; 6 [2; 10]) in contrast, the median (Q1; Q3) number of bleeds in patients in the twice-weekly not eligible for randomization group (n = 13) was 3.0 (2.0; 4.0) in the first 10 weeks.

After week 10 clinical assessment (weeks 11–36)

Following an increase to a median (Q1; Q3) dose of 39.0 (36.8; 40.5) IU kg⁻¹ BAY 94-9027 twice weekly, the median (Q1; Q3) ABR in patients in the twice-weekly not eligible for randomization group was substantially reduced, from 17.4 (14.3; 26.0) during the run-in period to 4.1 (2.0; 10.6) during weeks 11–36 (Fig. 4). In patients who were on prophylaxis before study start, the median (Q1; Q3) ABR in the previous 12 months was higher in patients in the twice-weekly not eligible for randomization group (12 [9; 16], n = 9) compared with patients who were eligible for randomization (twice-weekly eligible but not randomized, 5.5 [1; 13], n = 6; every 5 days, 3 [2; 10], n = 34; and every 7 days, 2 [1; 7], n = 37). Patients randomized to the every-5-days group achieved a low median (Q1; Q3) ABR during weeks 11–36 of 1.9 (0.0; 4.2); the median (Q1; Q3) number of bleeds during weeks 11–36 was 1.0 (0.0; 2.0). Those in the twice-weekly eligible but not randomized group also maintained a similarly low median (Q1; Q3) ABR (1.9 [0.0; 5.2]): the median (Q1; Q3) number of bleeds during weeks 11–36 was

Fig. 3. Number of infusions to control bleeds during the study (weeks 0–36). [Color figure can be viewed at wileyonlinelibrary.com]
1.0 (0.0; 3.0). The percentage of patients with 0 bleeds was also similar in the twice-weekly eligible but not randomized group and every-5-days group (46% and 44%, respectively, Table 2).

The median (Q1; Q3) ABR for patients in the every-7-days group was 3.9 (0.0; 6.5); the ABR was calculated for all patients assigned to the every-7-days regimen for the duration of time that they remained in the treatment arm (ITT population). The median (Q1; Q3) number of bleeds during weeks 11–36 for patients in the every-7-days group was 1.0 (0.0; 3.0). Thirty-seven per cent of patients treated every 7 days had 0 bleeds (Table 2). Eleven patients (26%) elected to leave the every-7-days group for more frequent dosing; eight patients chose dosing every 5 days and three patients chose twice-weekly prophylaxis (Table 3). Patients who opted to leave the every-7-days treatment group did so after a mean ± SD of 84 ± 38 days. Most patients who elected to leave the every-7-days group experienced ≥ 2 bleeds (range number of bleeds, 1–6) before changing dosing frequency, consistent with the protocol recommendation of making a change after ≥ 2 joint and/or muscle bleeds within any 10-week period. Comparison of the median (Q1; Q3) ABR for these patients showed that patients experienced an improvement in bleeding control from 16.9 (6.5; 25.2) before leaving the every-7-days group to 4.7 (0.0; 14.7) after changing to an every-5-days or twice-weekly regimen. The median (Q1; Q3) ABR for the 32 patients (74%) who remained in the every-7-days group for the full 26 weeks after randomization was 0.96 (0.0; 4.3) during weeks 11–36 (Table 3; Fig. 4); 50% of these patients experienced 0 bleeds (Table 2).

Safety

No inhibitors (FVIII ≥ 0.6 BU mL⁻¹) to BAY 94-9027 were detected during the study. One patient tested positive for a non-neutralizing antibody (NNA) to BAY 94-9027 at baseline; NNA titers declined over the course of the study and were negative at the final study visit. Five patients who tested negative at baseline had a positive NNA at different time-points during the study. No patient had a positive test at two consecutive visits and all patients had a negative test at the end of the study. NNAs in these five patients were all directed against PEG, not FVIII. No AEs or adverse effects on dose or bleeding were associated with NNAs in these patients.

Of the 134 patients exposed to BAY 94-9027 in the study, 100 patients (74.6%) reported ≥ 1 AE during treatment with BAY 94-9027. The types of AEs were representative of events occurring in the general hemophilia population [11,23–26]. The most common AEs (≥ 5%)
were nasopharyngitis (n = 24 [17.9%]), headache (n = 16 [11.9%]), arthralgia (n = 10 [7.5%]), back pain (n = 8 [6.0%]), cough (n = 8 [6.0%]) and epistaxis (n = 8 [6.0%]). AEs judged by the investigator to be related to BAY 94-9027 occurred in 12 patients (9%).

Two patients withdrew from the study because of reported brief and self-limited systemic hypersensitivity reactions, which occurred during the first exposure to BAY 94-9027 in one patient and following the fourth exposure in a second patient. In the second patient, an immunoglobulin M (IgM) antibody directed against the PEG component of the molecule was detected 4 days after the reaction. The antibody was low titer and became undetectable 1 month later.

Discussion

BAY 94-9027 is B-domain-deleted rFVIII with site-specific PEGylation for a prolonged half-life [14]. The PROTECT VIII trial demonstrated that treatment with BAY 94-9027 is efficacious as prophylaxis with dosing intervals up to every 7 days and also for the treatment of acute bleeds. The unique individualized study design allowed patients who demonstrated good bleed control on twice-weekly dosing to adjust their dosing schedule to longer intervals between infusions. This design reflects the real-world clinical approach to prophylaxis in which dosing regimens are tailored with the goal of optimizing bleed control using infusion schedules that best fit the needs of individual patients.

Although FVIII levels and PK parameters are associated with bleeding risk [6], many other factors are also involved [16,17]. Phenotype-guided dosing is based on the overall bleeding pattern in each individual patient. Results from the Canadian Hemophilia Primary Prophylaxis Study, which was performed using a dose-escalation prophylaxis regimen tailored to individual patient responses, suggest that some patients have few bleeds with once-weekly prophylaxis using a standard half-life FVIII product [10,27,28]. Using a run-in period with twice-weekly dosing to identify patients with lower bleeding risk, our study also showed good bleed control in patients treated prophylactically with BAY 94-9027 every 5 or 7 days.

After the 10-week run-in period of twice-weekly dosing, the vast majority of patients experienced ≤1 bleed and qualified for randomization for dosing every 5 or 7 days. All 43 patients randomized to the every-5-days prophylaxis group remained in that treatment arm and had a low median ABR of 1.9; 44% of these patients experienced 0 bleeds during the following 26-week study period. The 11 patients who continued with twice-weekly prophylaxis because the randomization arms were filled had a similarly low bleeding rate.

Although PK modeling from the phase 1 study with BAY 94-9027 suggested that only 15% of patients may maintain FVIII trough levels above 1% with every-7-days dosing [14], we found that BAY 94-9027 administered every 7 days provided effective prophylaxis for the majority of patients randomized to that treatment arm. Of patients randomized to every-7-days treatment, almost three-quarters of the patients remained in the treatment group for the duration of the study; these 32 patients had a low median ABR of 0.96, and half experienced 0 bleeds during weeks 11–36. Only 11 patients (26%) left the every-7-days group because of inadequate bleed control; the majority of these patients transitioned to every-5-days prophylaxis. Overall, patients who left the every-7-days group experienced a substantial improvement in ABR after transitioning to a more frequent dosing regimen, which underscores the importance of an individualized prophylaxis regimen as used in our study. We conclude from these data that specific knowledge of individual patients’ bleeding history may help identify those who benefit from less frequent infusions with BAY 94-9027. Our findings demonstrate that individually tailored prophylaxis regimens can provide effective bleed control.

Patients who were not good candidates for an extended dosing interval were identified during the run-in period before randomization. These patients remained on twice-weekly dosing for the remaining 26 weeks of the study, but their dose was increased from 25 to 30–40 IU kg⁻¹. Following the dose increase during study weeks 11–36, the ABR was substantially reduced in these patients, demonstrating that better bleed control can be achieved with BAY 94-9027 in these difficult-to-manage patients who may require higher trough levels.

Table 3 Bleeding summary in randomized patients

| Number of total bleeds | Every 5 days (n = 43) | Every 7 days (n = 32) | Left every-7-days treatment arm |
|------------------------|----------------------|----------------------|----------------------------------|
| Mean ± SD              | 1.6 ± 2.1            | 1.3 ± 1.9            | 3.1 ± 2.0                        |
| Median (Q1; Q3)        | 1.0 (0; 2.0)         | 0.5 (0; 2.0)         | 2.0 (2.0; 6.0)                   |
| ABR                    | 1.93 (0; 4.2)        | 0.96 (0; 4.3)        | 16.86 (6.5; 25.2)                |

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The open-label design and subjective nature of the patient-reported assessment of treatment of bleeds are potential limitations of the study. However, we believe that the study design reflects the real-world clinical setting and heterogeneity of the patient population. Specific strengths of the present study are the well-defined run-in period and subsequent randomization to two different treatment arms. For the assessment of the long-term efficacy and safety of BAY 94-9027, an optional extension study (≥6 months) has been initiated and is currently ongoing.

Conclusions

The PROTECT VIII study achieved its primary objective: the prolonged half-life of BAY 94-9027 provided prevention of bleeding at dose intervals up to every 7 days. Effective prophylaxis was also demonstrated with administration of BAY 94-9027 twice weekly and every 5 days; thus, the prophylaxis dose and dosing regimen can be tailored to the patient’s individual bleeding tendency. BAY 94-9027 was also effective in the treatment of bleeds, with approximately 90% of bleeds controlled with ≤2 infusions. Treatment with BAY 94-9027 was generally well tolerated and no patient developed inhibitors to FVIII during the study. Less frequent prophylaxis dosing with BAY 94-9027 (up to every 7 days in some patients) using an individualized approach based on patient response is an effective strategy in the management of patients with severe hemophilia A.

Addendum

M. T. Reding, H. J. Ng, M. Lederman, and L.A. Michaels contributed to data acquisition, data interpretation and data analysis. L. H. Poulsen, M. E. Eyster, H.-J. Shin, and R. Walsch contributed to data collection. I. Pabinger contributed to data acquisition and data interpretation. M. Wang contributed to data interpretation and analysis. M. Hardtke contributed to data interpretation. All authors contributed to the development of the manuscript, reviewed and commented on each draft, and approved the final draft.

Acknowledgements

This study was funded by Bayer Pharma AG, Leverkusen, Germany. Medical writing assistance was provided by K. Wannemacher from Complete Healthcare Communications, LLC (Chadds Ford, PA, USA), and was funded by Bayer.

Disclosure of Conflict of Interests

M. T. Reding has received honoraria from Baxalta, Biogen, Novo Nordisk and Pfizer, has served as a consultant for Biogen, and has served on advisory committees for Bayer, Biogen, Baxalta and Novo Nordisk. L. H. Poulsen has served on advisory committees for Bayer and Pfizer, has acted as a clinical trial investigator for Bayer and Novo Nordisk, and has received personal fees for lectures from Ferring. M. E. Eyster has been contracted to participate in studies for Bayer. I. Pabinger has received honoraria for occasional lectures from Bayer. M. Lederman, M. Wang, and L. A. Michaels are employees of Bayer. R. Walsch is an employee of Bayer Vital GmbH. M. Hardtke is an employee of Bayer Pharma AG. H.-J. Shin and H. J. Ng state that they have no conflict of interest.

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