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Full Length Article

Safety and efficacy of BAY 94-9027, an extended-half-life factor VIII, during surgery in patients with severe hemophilia A: Results of the PROTECT VIII clinical trial

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ABSTRACT

Introduction: Ensuring hemostasis during invasive procedures is a challenge in patients with severe hemophilia A. This analysis evaluated efficacy and safety of BAY 94-9027, an extended-half-life recombinant factor VIII (FVIII), in the surgical setting.

Materials and methods: Patients participating in an open-label BAY 94-9027 clinical trial who underwent major surgery were included in the analysis. Investigator/surgeon assessment of hemostasis during surgery was the primary outcome. In addition, information about FVIII use, FVIII levels during perioperative period, bleeding complications and FVIII inhibitor development were collected.

Results: Data were analyzed for 26 major surgeries (orthopedic, n = 21) in 20 patients aged 13–61 years. BAY 94-9027 provided effective hemostasis during all procedures. FVIII levels 6–8 h post preoperative infusion and prior to the first follow-up infusion were in the range expected to maintain protection in the major surgery setting. The median time from preoperative infusion to the first follow-up infusion (the first infusion administered after the preoperative infusion) was 12.33 (3.6–49.9) h. No intraoperative bleeding complications occurred, and no new inhibitors developed following any surgery.

Conclusions: The results of the study demonstrate that BAY 94-9027 was efficacious and well tolerated in the treatment of patients undergoing major surgeries. Advantages of BAY 94-9027 include the potential for less frequent infusion and reduced factor consumption, which should simplify the management of patients during major surgery.

1. Introduction

In patients with hemophilia A, surgery represents a major challenge as it is inherently associated with the potential for excessive and uncontrolled bleeding. Major surgery often necessitates intensified factor VIII (FVIII) replacement to maintain hemostasis and adequate FVIII plasma levels until wound healing occurs [1–4]. In contrast to standard-acting FVIII products, which usually require frequent factor administration or continuous infusion [5–7] to provide adequate hemostatic control, extended-half-life FVIII products may enable the maintenance of the desired threshold level for longer.

BAY 94-9027 (Jivi®; Bayer, Berkeley, CA, USA) is a B-domain-deleted (BDD) rFVIII that is site-specifically conjugated with a 60-kDa branched polyethylene glycol (PEG) at a cysteine that has been introduced into the A3 domain (K1804C) resulting in 1 PEG per BDD-rFVIII protein [8,9]. Pharmacokinetic (PK) data show that BAY 94-9027

Abbreviations: AE, adverse event; BDD, B-domain-deleted; BU, Bethesda units; FVIII, factor VIII; PEG, polyethylene glycol; PK, pharmacokinetic

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has increased area under the curve (AUC) and longer half-life through reduced plasma clearance compared with standard-acting rFVIII [8]. BAY 94-9027 is expected to provide effective hemostasis with optimal FVIII activity coverage over a longer period in patients undergoing surgery, resulting in higher trough levels so that fewer infusions may be needed. This has added advantages of providing potential for lower FVIII consumption (usage), improved convenience and reduced duration of hospitalization.

The objective of this study was to evaluate the safety and efficacy of BAY 94-9027 for the prevention of bleeding during major surgery in adults and adolescents with severe hemophilia A.

2. Materials and methods

2.1. Patients and demographics

This open-label study enrolled severe hemophilia A (FVIII:C < 1%) patients aged 12 to 65 years with no FVIII inhibitors (current and historical inhibitor titers < 0.6 Bethesda units [BU]), previously treated with any FVIII product for ≥150 exposure days. Eligible patients were receiving BAY 94-9027 in the PROTECT VIII clinical trial [10] (ClinicalTrials.gov identifier: NCT01580293) or were not participating in PROTECT VIII but required major surgery and met the PROTECT VIII inclusion criteria. Key exclusion criteria included platelet count < 100,000/mm^3, creatinine > 2 times the upper limit of normal (ULN), aspartate aminotransferase or alanine aminotransferase > 5 times ULN.

Baseline characteristics of the participating patients were collected, including age, race and weight. Informed consent for participation in the study was provided by patients or their legal guardians, and the protocol was approved by each site's independent ethics committee/institutional review board (AppendixA).

2.2. Treatment

Major surgery was defined by the presence of any of the following criteria:

- A surgical procedure in which the overall bleeding risk may be excessive
- Requirement for general anesthesia in an individual without a bleeding disorder
- Penetration or exposure of a major body cavity
- Potential to result in substantial impairment of physical or physiologic functions.

Patients undergoing surgery were treated according to the type of procedure, using doses and frequency of dosing expected to maintain targeted levels of FVIII activity based on standard recommendations [11]. The protocol recommended that decisions of the dose and frequency of administration be based on the result of local laboratory evaluation to target desired FVIII activity. Treatment decisions from the time of surgery until the patient left the hospital were made by the treating physician. Patients received BAY 94-9027 as their only factor VIII replacement product until discharge from hospital when they switched to their prior treatment product. Patients in the PROTECT VIII trial continued using BAY 94-9027 as per protocol assignment. The remaining patients switched to their commercial FVIII products.

2.3. Outcome measures

The primary outcome was assessment at the end of the surgery of the effectiveness of BAY 94-9027 in providing bleeding control. The surgeon was asked to compare the outcome with expected blood loss in patients without hemophilia undergoing comparable procedures using a 4-point scale:

- Excellent: blood loss less than expected
- Good: blood loss as expected
- Moderate: blood loss more than expected
- Poor: uncontrolled bleeding.

Data collected to allow for clinical confirmation of the surgeon/physician assessment of hemostasis included the need for transfusions during the perioperative period until 24 h post-surgery, estimated blood loss during surgery, use of anti-fibrinolytics or thromboprophylaxis and any intraoperative complications secondary to bleeding.

2.4. FVIII measurements and BAY 94-9027 usage

As part of study participation, all patients were required to undergo PK evaluation prior to surgery, in which samples were collected over a 24-h period. These were analyzed in both the local and central laboratories. The study sites used their usual and locally available laboratory methods for measurement of the FVIII activity of BAY 94-9027. The protocol recommended that individualized decisions regarding the doses given and the frequency of administration of BAY 94-9027 should be based on the local preoperative PK results. The samples analyzed in the central laboratory were used to confirm accuracy of the samples analyzed locally and were only made available to the site if specifically requested.

To determine if the PK of BAY 94-9027 during surgery were similar to those predicted by the preoperative PK in the non-bleeding state, additional samples were collected before the preoperative infusion, at 6–8 h and either at 24 h or prior to first follow-up infusion (the first infusion administered after the preoperative infusion). FVIII levels using measurements from the central laboratory were used to make the comparison. In addition, these values allowed for assessment of whether the FVIII levels achieved were in the recommended ranges for the type of surgery [11].

The following information was collected to assess use of BAY 94-9027:

- Preoperative dose
- The time between the preoperative infusion and the first follow-up infusion (intraoperative or postoperative)
- Need for additional dosing during the procedure
- Total dose of BAY 94-9027 and number of infusions on the day of surgery (including preoperative, intraoperative, and postoperative infusions until midnight on the day of surgery) in order to assess the intensity of treatment on that day
- BAY 94-9027 use for the first 24 h period after the end of surgery
- Total BAY 94-9027 dose during hospitalization period and number of hospitalization days.

2.5. Safety assessment

The primary safety outcome was the occurrence of bleeding complications during surgery. Analysis of overall adverse event reporting was also performed.

Samples to assess FVIII inhibitor measurements (Bethesda assay) and the presence of anti-BAY 94-9027 or anti-PEG antibodies were collected at screening (baseline), at the PK assessment visit before BAY 94-9027 infusion, at surgery before the preoperative dose, and at the postoperative visit 1–2 weeks after hospital discharge.

3. Results

3.1. Patients and demographics

The baseline characteristics for all patients who underwent major surgery are shown in Table 1. A total of 5 (25%), 7 (35%) and 14 (70%) patients were positive for human immunodeficiency virus (HIV),

Table 1
Patient characteristics at time of surgery.

Patient number and type of surgery	Age at time of consent (years)	Race	Weight at time of consent (kg)
1-Shoulder arthroscopy and subacromial decompression	42	White	99.8
2-Total knee arthroplasty	33	White	115.5
3-Open repair of recurrent inguinal and umbilical hernias	45	White	77.2
4-Total hip arthroplasty	51	White	76.0
5-Placement of infrapubic 3-piece inflatable penile prosthesis	51	White	74.0
6-Arthroscopic subtalar fusion[a]	28	White	79.4
6-Subtalar arthroscopy and fusion[a]	28	White	81.0
7-Removal of knee prosthesis[b]	61	Not reported	70.0
7-Re-implantation of knee prosthesis[b]	61	Not reported	70.0
7-Ankle prosthesis[b]	61	Not reported	65.0
8-Knee replacement	37	White	63.0
9-Knee arthroplasty re-implantation	41	White	81.0
10-Ankle arthroplasty	32	White	93.0
11-Total knee replacement	57	White	74.0
12-Total knee replacement[c]	37	White	81.4
12-Total knee replacement[c]	37	White	81.8
13-Total ankle replacement	30	White	90.0
14-Impacted and simple tooth extraction	24	White	85.0
15-Total knee replacement	30	White	64.0
16-Total knee replacement	33	White	78.6
17-Knee/thigh synovectomy and Judet plus soft-tissue release[d]	25	White	55.0
17-Emergency knee/thigh hematoma evacuation[d]	25	White	55.0
18-Arthroscopic synovectomy	33	Asian	65.0
19-Knee synovectomy	13	White	50.0
20-Extraction of 2 teeth and alveoloplasty[e]	26	White	95.5
20-Extraction of 3 teeth and alveoloplasty[e]	26	White	94.0

[a,c,d,e]4 patients each had 2 surgeries.
[b]1 patient had 3 surgeries.

hepatitis B virus (HBV) and hepatitis C virus (HCV), respectively, at baseline. Table 2 shows the type of surgery, procedure duration, assessment of hemostasis, and whether additional treatment was needed. Table 3 shows PK outcomes and postoperative dosing. In total, 20 patients aged 13–61 years underwent 26 major surgeries. Ten patients were participants in the PROTECT VIII clinical trial and 10 were not. Patients were treated in 11 study sites from 9 countries. Four patients had 2 major surgeries and 1 patient had 3 major surgeries.

The 26 major surgeries included 21 orthopedic surgeries (1 hip replacement, 10 knee replacements and 3 ankle replacements, 2 open synovectomies, 4 arthroscopic procedures, and 1 knee/thigh hematoma evacuation), 3 complex dental extractions, and 2 other procedures (penile prosthesis and inguinal hernia repair).

3.2. Surgical outcomes

The primary endpoint of surgeon/physician assessment of hemostasis during surgery and data collected to support this assessment, such as need for transfusions during perioperative period until 24 h post-surgery and the estimated blood loss during surgery, are reported in Table 2.

Hemostasis during surgery was assessed as good (17/26) or excellent (9/26) for all surgeries, indicating that blood loss was as expected, or less than expected, in comparison with similar procedures in non-hemophilia patients.

Blood transfusion during or immediately following surgery was given to 3 patients, 2 patients undergoing knee replacement (patients 7 and 9) and 1 patient undergoing knee synovectomy and Judet procedure (patient 17). FVIII levels measured in the perioperative period in these 3 patients were in the range expected to provide adequate hemostasis (Table 3), with need for transfusion as expected for the type of surgery.

As part of routine care to prevent bleeding, anti-fibrinolytic medications were used in 12 surgeries (11 orthopedic surgeries and 1 complex tooth extraction). Use was independent of bleeding risk, and performed as per local treatment preferences. In addition, thromboprophylaxis was used only by patient 11, who received nadroparin during the perioperative period.

3.3. FVIII measurements and BAY 94-9027 usage

Treatment decisions and total drug consumption were variable, owing to heterogeneity in the local standard of care. In all cases treatment was individualized, and dependent upon patient characteristics, the type of surgical procedure and duration of hospitalization.

The mean ± SD AUC normalized and half-life in the preoperative PK assessment were 65.57 (29.85) kg∗h/dL and 17.28 (6.36) h, respectively. The results of FVIII levels measured around the time of surgery are reported in Table 3 and were consistent with those predicted by the preoperative PK measurements. No differences were observed in the BAY 94-9027 profile during surgery as compared to the non-bleeding state (data not shown).

BAY 94-9027 use on the day of surgery and during the first 24 h of postoperative period is reported in Tables 2 and 3. Total BAY 94-9027 dose during hospitalizations is reported in Table 3.

The mean ± SD administered BAY 94-9027 preoperative dose was 53.2 ± 5.8 (median [range], 52.9 [41–64]) IU/kg. FVIII levels 6–8 h post preoperative infusion were within the guideline-recommended ranges for major surgeries [11]. The mean ± SD total dose administered on the day of surgery was 76.8 ± 25.4 (median [range], 77.57 [42.9–136.4]) IU/kg. The median (range) time from preoperative infusion to the first follow-up infusion was 12.33 (3.6 to 49.9) h. In all but one case, the first follow-up infusion was administered after the surgery was completed, and in the recovery period. One patient was treated intraoperatively, 3.6 h after the first infusion, 90 min into the procedure. This patient was known to have a significantly reduced recovery and half-life as part of the preoperative PK measurements. Details on this one patient are discussed below (patient 17).

FVIII levels collected prior to the first follow-up infusion were also within the guideline-recommended ranges in most of the cases [11].

3.4. Safety

The primary safety outcome was met as there were no reported

Table 2
Details of major surgeries with clinical outcomes and pre/perioperative dosing.

Patient number and type of surgery	Duration of surgery	Estimated blood loss during surgery (mL)	Assessment of hemostasis during surgery	Bleeding/anemia reported during surgery or up to 24 h post-surgery?	Blood transfusion needed up to 24 h post end of surgery	Preoperative BAY 94-9027 dose (IU/kg)	Need for BAY 94-9027 intraoperative infusion	Total number of BAY 94-9027 infusions on the day of surgery[a]
1. Shoulder arthroscopy and subacromial decompression	1 h 5 min	0	Good		No	50.1	No	1
2. Total knee arthroplasty	1 h 43 min	100	Good		No	51.9	No	2
3. Open repair of recurrent inguinal and umbilical hernias	1 h 0 min	50	Excellent		No	51.5	No	2
4. Total hip arthroplasty	1 h 45 min	250	Excellent	Postoperative anemia	No	52.6	No	2
5. Placement of infrapubic 3-piece inflatable penile prosthesis	1 h 36 min	50	Good		No	47.3	No	2
6. Arthroscopic subtalar fusion[b]	2 h 44 min	5	Good		No	50.4	No	1
6. Subtalar arthroscopy and fusion[b]	2 h 4 min	20	Good		No	49.4	No	1
7. Removal of knee prosthesis[c]	1 h 55 min	590	Excellent		No	57.1	No	1
7. Re-implantation of knee prosthesis[c]	2 h 59 min	1000	Good		Yes	42.9	No	1
7. Ankle prosthesis[c]	1 h 56 min	300	Good		No	61.5	No	1
8. Knee replacement	1 h 40 min	0	Good	Bleeding at surgical site	No	55.6	No	2
9. Knee arthroplasty re-implantation	2 h 40 min	400	Good	Low hemoglobin	Yes	49.4	No	2
10. Ankle arthroplasty	2 h 10 min	500	Good		No	53.8	No	2
11. Total knee replacement	3 h 3 min	0	Good		No	40.5	No	2
12. Total knee replacement[d]	1 h 40 min	300	Good		No	61.4	No	2
12. Total knee replacement[d]	0 h 45 min	300	Excellent		No	61.1	No	2
13. Total ankle replacement	3 h 37 min	150	Good		No	55.6	No	2
14. Impacted and simple tooth extraction	0 h 30 min	10	Excellent		No	47.1	No	1
15. Total knee replacement	1 h 45 min	250	Good		No	62.5	No	2
16. Total knee replacement	1 h 20 min	200	Excellent		No	57.3	No	2
17. Knee/thigh synovectomy and Judet plus soft-tissue release[e,f]	1 h 44 min	1000	Good	Low hemoglobin	Yes	63.6	Yes	3
17. Emergency knee/thigh hematoma evacuation[e,f]	1 h 44 min	600	Good		Yes	54.5	No	2
18. Arthroscopic synovectomy[g]	1 h 35 min	30	Good		No	53.8	No	3
19. Knee synovectomy	0 h 17 min	30	Excellent		No	50.0	No	1
20. Extraction of 2 teeth and alveoloplasty[h]	1 h 13 min	10	Excellent		No	49.9	No	1
20. Extraction of 3 teeth and alveoloplasty[h]	0 h 36 min	7	Excellent		No	53.2	No	1

[a]Includes preoperative, any intraoperative and postoperative infusions on the day of surgery until 0 h of the following day.
[b,d,e,h]4 patients each had 2 surgeries.
[c]1 patient had 3 surgeries.
[f]Patient had preoperative inhibitor (0.5 BU).
[g]Patient had inhibitor (1.7 BU) in sample collected immediately before surgery.
BU, Bethesda units; h, hours; min, minutes.

Table 3
Details of major surgeries with pharmacokinetic outcomes and postoperative dosing.

Patient number and type of surgery	Time between preoperative infusion and next infusion (h)	FVIII level 6–8 h post preoperative infusion (IU/dL)	FVIII level before next infusion (IU/dL)[a]	BAY 94-9027 dose on the first 24 h post end of surgery	Number of BAY 94-9027 infusions on the first 24 h post end of surgery	Total BAY 94-9027 dose during hospitalization[b] (IU/kg)	Number of hospitalization days
1. Shoulder arthroscopy and subacromial decompression	21.9	97.5	76.3	40.1	1	90.2	2
2. Total knee arthroplasty	12.8	185.8	130.8	26.0	1	181.81	5
3. Open repair of recurrent inguinal and umbilical hernias	12	83.3	60.7	51.5	2	181.34	4
4. Total hip arthroplasty	8.3	81.1	71.6	157.9	3	394.7	7
5. Placement of infrapubic 3-piece inflatable penile prosthesis	12.3	115.8	84.6	40.5	2	128.4	3
6. Arthroscopic subtalar fusion[c]	24.4	113.1	NA	37.8	1	50.4	1
6. Subtalar arthroscopy and fusion[c]	23.8	75.6	53.3	37.0	1	49.4	1
7. Removal of knee prosthesis[d]	18.2	139.3	85.7	42.9	2	785.7	30
7. Re-implantation of knee prosthesis[d]	23.9	122.3	62.7	28.6	1	671.4	21
7. Ankle prosthesis[d]	24.1	93.0	29.9	46.2	1	461.5	22
8. Knee replacement	13.6	78.0	55.5	23.8	1	333.3	11
9. Knee arthroplasty re-implantation	10.0	68.0	59.2	61.7	2	209.9	5
10. Ankle arthroplasty	12.3	101.2	44.2	48.4	2	166.7	6
11. Total knee replacement	8.0	90.3	77.5	54.1	2	337.8	11
12. Total knee replacement[e]	6.0	122.2	122.2	73.7	2	774.0	18
12. Total knee replacement[e]	6.2	123.6	123.6	73.3	2	281.2	5
13. Total ankle replacement	6.7	139.8	139.8	100.0	2	222.2	4
14. Impacted and simple tooth extraction	24.2	114.1	61.2	23.5	1	70.6	2
15. Total knee replacement	6.3	104.7	104.7	62.5	2	500.0	10
16. Total knee replacement	7.1	127.9	127.9	76.3	2	248.1	6
17. Knee/thigh synovectomy and Judet plus soft-tissue release[f,g]	3.6	102.9	NA	72.7	2	1500.0	17
17. Emergency knee/thigh hematoma evacuation[f,g]	10.0	NA	NA	181.8	3	236.4	16
18. Arthroscopic synovectomy[h]	9.5	8.99	NA	84.6	3	215.4	6
19. Knee synovectomy	25.3	81.0	NA	0	0	710.0	22
20. Extraction of 2 teeth and alveoloplasty[i]	47.5	167.7	NA	0	0	128.5	8
20. Extraction of 3 teeth and alveoloplasty[i]	49.9	77.6	NA	0	0	79.8	5

NA, not available.
[a]Chromogenic assay performed by the central lab. FVIII levels are reported if collected within 1 h prior to the first infusion applied after the preoperative infusion.
[b]BAY 94-9027 total dose for infusions related to major surgery during entire hospitalization period.
[c,e,f,i]4 patients each had 2 surgeries.
[d]1 patient had 3 surgeries.
[g]Patient had preoperative inhibitor (0.5 BU).
[h]Patient had inhibitor (1.7 BU) in sample collected immediately before surgery.
BU, Bethesda units; h, hours.

events associated with bleeding complications during surgery.

Adverse events (AEs) were reported in 19 patients, with the majority assessed as unrelated to the study drug. Three patients had study drug-related AEs as judged by the investigator. One patient (patient 11) had a subcutaneous hematoma in the surgery site (operated knee), which was successfully treated with an additional dose of BAY 94-9027; concurrent nadroparin prophylaxis for thrombosis was administered as part of local standard of care.

The other 2 patients with study drug-related AEs (patients 17 and 18) had low titer anti-FVIII antibodies, detected in the blood sample collected immediately before surgery. Patient 18 had a one-time measurement of 1.7 BU in the sample collected immediately prior to surgery; this was not confirmed on repeat testing. Although FVIII at 6–8 h after the preoperative infusion was below expected (8.99%), hemostasis during surgery was considered good, with limited blood loss reported intraoperatively.

Patient 17 had a known history of poor recovery and short half-life measured after treatment with other FVIII products and, at study enrollment, the Bethesda assay measurement was 0.5 BU mL^{-1}, which did not meet the protocol exclusion criteria of > 0.6 BU mL^{-1}. Although the recovery and half-life measured preoperatively with BAY 94-9027 were also reduced, the decision to treat with study drug was based on a better PK profile as compared to his prior product. In the sample collected prior to surgery, a low titer anti-FVIII antibody of 0.6 BU mL^{-1} was confirmed. The patient underwent one planned surgery using BAY 94-9027, during which hemostasis was assessed as good. During the postoperative period, FVIII trough levels were maintained within the range of 42–136 IU/dL. However, the patient developed a hematoma in the operated thigh and a second surgery for hematoma evacuation was performed 14 days after the first surgery. Hemostasis during surgery was also assessed as good and no intraoperative complications were reported. He received a total of 95,500 Units of BAY 94-9027 during hospitalization with no change in his anti-FVIII antibody titer. This was the only patient who needed to return to the operating theater during the postoperative period.

No new confirmed FVIII inhibitors (FVIII ≥ 0.6 BU mL^{-1}) developed following surgery. No vascular thrombotic events were reported. No patient developed anti-BAY 94-9027 or anti-PEG antibodies. Anaphylaxis or hypersensitivity associated with loss of treatment response was not observed.

4. Discussion

This analysis demonstrates that BAY 94-9027 was well tolerated and efficacious during the perioperative period. This cohort includes the largest number of major surgeries to date performed in hemophilia A patients using an extended-half-life FVIII product. The cohort represents a diverse group of patients treated in 9 countries from Asia, Europe and North America, and thus reflects the wide variability in types of surgery and different local practices. As such, the experiences collected using BAY 94-9027 in this study are applicable to use in the general population of patients with severe hemophilia A.

A total of 26 major surgeries were evaluated, the majority of which were orthopedic (81%), with many of the procedures associated with either a high immediate bleeding risk during surgery, or risk of bleeding in the recovery period. The results reported here show that hemostatic control was good to excellent in all cases, including one patient with a low titer inhibitor and reduced treatment response to other FVIII products. Satisfaction with the efficacy of BAY 94-9027 is also suggested as 4 patients in this study had repeat surgeries; no patients switched to a different product for subsequent surgery because of inadequate treatment concerns.

Due to the small sample sizes, heterogeneity of procedures and distinctive ways information about FVIII usage is collected across studies in this setting, it is challenging to make comparisons across different products regarding FVIII consumption and frequency of infusion. Nevertheless, BAY 94-9027 consumption on the day of major surgery was similar or even slightly lower (range, 42.9–136.4 IU/kg) compared with standard-acting FVIII products, including turoctocog alfa (range, 27–153 IU/kg) and unmodified full-length rFVIII (Kovaltry®; range, 59.5–207.3 IU/kg) [6,12]. In addition, the number of perioperative BAY 94-9027 infusions (range, 1–3 infusions) and dose on the day of surgery was similar to other extended-half-life rFVIII products; such as rFVIIIFc (Eloctate®; range, 50.8–126.6 IU/kg) and N8-GP (range, 50.5–136.2 IU/kg) [13,14].

One limitation of the study is the heterogeneity in surgery indications, which may affect perioperative care and length of hospital stay, leading to variability in BAY 94-9027 consumption during the postoperative period. Another limitation is the heterogeneity in the local standard of care; treatment decisions including the dose required, frequency of infusion and use of supportive medications, such as anti-fibrinolytics, were ultimately determined by the investigator.

The ability to measure FVIII activity is of paramount importance for the preparation and management of major surgeries of hemophilia patients [2]. Preoperative PK testing enabled an accurate prediction of the dose required and predicted the FVIII levels that would be achieved to provide perioperative bleed protection. In all cases, the FVIII levels obtained were within guideline-recommended ranges. Importantly, all study sites were required to measure FVIII levels in the local laboratory. Our data confirm that all sites were able to appropriately monitor BAY 94-9027. Treatment decisions based on local assay methods resulted in the achievement of protective FVIII levels during the perioperative period. Additionally, FVIII levels collected before surgery in the non-bleeding state were similar to those measured around the time of surgery, confirming that dosing decisions based on the preoperative PK assessment were appropriate to predict behavior during surgery.

5. Conclusions

In summary, in 26 major surgeries, BAY 94-9027 was observed to provide adequate hemostatic coverage and to be efficacious with a good safety profile for the prevention of bleeding during major surgeries in individuals with severe hemophilia A. Advantages of BAY 94-9027 included potential for less frequent infusion and reduced factor consumption.

Declaration of competing interest

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Speaker bureau: Bayer, Shire, CSL Behring, Novo Nordisk, Roche, Grifols, Kedrion, Octapharma, Pfizer, Sobi and Bioverativ.
Advisory board participation: Bayer, Shire, CSL Behring, Novo Nordisk, Roche, Grifols, Kedrion, Octapharma, Pfizer, Sobi and Bioverativ.

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Appendix A

The protocol was approved by each site's independent ethics committee/institutional review board (1429/2012, Dr Pabinger Fasching, Vienna, Austria; EudraCT Number: 2011-005210-11 [Internal Number 1246], Dr Claude Negrier, Lyon, France; STH16384 (CSP 97241), Dr Kingsley Hampton, Sheffield, UK; 9224-12-SMC, Dr Shadam Lalezari, Tel HaShomer, Israel; EudraCT Number: 2011-005210-11, Dr Elena Santagostino, Milan, Italy; ABR Number: NL40664.042.12, Dr Karina Meijer, Rotterdam, The Netherlands; 3882, 2820, Dr Margit Serban, Timișoara, Romania; 2012-05-002A, Dr Yuan Bin Yu, Taipei, Taiwan; 367742-3, Dr Jonathan Ducore, Sacramento, CA, USA; 39700 [Bayer 13024], Dr M Elaine Eyster, Hershey, PA, USA; 357407-2, Dr Thomas Coyle, Cincinnati, OH, USA).

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