Table 1: Patient demographics and baseline characteristics (n = 631).

Mean age (SD), years[a]	23.7 (16.6)
Gender, n (%)	
Male	628 (99.5)
Female	1 (0.2)
No information	2 (0.3)
FVIII activity, n (%)	
<1%	426 (67.5)
1%-2%	79 (12.5)
>2%-5%	64 (10.1)
>5%	56 (8.9)
No information	6 (1.0)
Exposure days (EDs) prior to study, n (%)	
0 (PUPs)	17 (2.7)
1–19	45 (7.1)
20–100	59 (9.4)
>100	477 (75.6)
No information	33 (5.2)
Previous treatment product, n (%)[b]	
Recombinant FVIII	355 (59.9)
Plasma-derived FVIII	194 (32.7)
Non-FVIII product	2 (0.3)
Missing	42 (7.1)
History of inhibitors, n (%)	
Positive history (total)	32 (5.1)
Peak level ≤5 BU	19 (3.0)
Peak level >5 BU	11 (1.7)
No peak-level information	2 (0.3)
Inhibitors at baseline, n (%)	
Positive at baseline (total)	8 (1.3)
Low titre (<5 BU)	4 (0.6)
High titre (≥5 BU)	2 (0.3)
No titre information	2 (0.3)
Known seropositive status, n (%)	
Hepatitis A	9 (1.4)
Hepatitis B	112 (17.7)
Hepatitis C	311 (49.3)
HIV	86 (13.6)
Target joint specified, n (%)	365 (57.8)

SD, standard deviation; BU, Bethesda units; PUPs, previously untreated patients. [a]n = 629, [b]n = 593.

order of mean frequency per patient per year, were prophylaxis, joint bleeds, other bleeds, or surgery (Table 2). The mean number of infusions and mean total consumption of rFVIII-FS per patient for each of these reasons, for the total population as well as for the 111 (17.6%) subjects who received regular prophylaxis, are summarized in Table 2.

Bleeding events

On average, the mean number of follow-up treatments (± SD) required to manage joint bleeding episodes was 1.1 (± 1.5) and for other bleeding episodes, 1.2 (± 3.3). The results of follow-up treatments of bleeding episodes for patients on regular prophylaxis did not significantly differ from those of the total sample.

Efficacy assessment

At the end of the observation period, the efficacy of rFVIII-FS was globally evaluated for each patient by the physician; assessment data was available for 630 of 631 evaluable patients. Efficacy of treatment was rated "very good" in 409 (64.8%) patients, "good" in 219 (34.7%) patients, and "sufficient" in two (0.3%) patients. No cases were rated "insufficient"; an efficacy assessment was not available for one (0.2%) patient. Overall, the efficacy of rFVIII-FS was rated "very good" or "good" in 99.5% (628/631) of evaluable patients.

Safety evaluation

The safety analysis included data for the 631 eligible patients. Fifteen AEs were reported in 15 different patients. These included seven cases of inhibitor development, one non-serious case of a drug-related allergy, and seven serious non-drug-related SAEs. Four deaths occurred during the observation period due to lymphoma, cerebral haemorrhage, hepatic embolization, and ruptured liver carcinoma, respectively. All patient deaths were assessed as unrelated to rFVIII-FS by the investigator.

Inhibitor development

Positive inhibitor tests were detected and reported for seven patients during the study: five with *de novo* inhibitor formation, one with a persistent (fluctuating) inhibitor, and one with recurrent inhibitor development (Table 3).

Overall, there were five patients with *de novo* inhibitors in the total study population, giving an incidence of 0.8% (5/631). Data for 33 patients was insufficient to classify them among a particular pre-treatment group. Among all patients with <20 EDs at enrollment who were considered to be at highest risk for new inhibitor development, the *de novo* inhibitor rate was two in 62 (3.2%). Both cases occurred in severe haemophilia A patients (n = 35; 5.7% among patients with <1% FVIII:C) who were minimally treated at enrollment. No positive inhibitor titre was reported in any of the 17 PUPs. Among patients with 20–100 EDs at enrollment who are still at risk for inhibitor formation, two in 59 (3.4%) developed a *de novo* inhibitor (the inhibitors were transient in both patients). Both patients had severe haemophilia, making the rate in this subgroup two in 29 (6.9%). Among patients with >100 EDs at enrollment who are considered to be at low risk for new inhibitor development, *de novo* inhibitors were observed in one of 477 patients (0.2%) overall, and one in 344 (0.3%) of the severe patient subset.

Limiting the analysis to only the 599 patients with no known history of inhibitors and negative titre at baseline, the incidence is 0.8% (5/599) overall and 1.3% (5/399) among patients with <1% baseline FVIII:C. Within the no previous inhibitor group, the *de novo* inhibitor rate among the highest risk patients (<20 EDs at enrollment) was 3.5% (2/57) for all patients and 6.7% (2/30) excluding those with ≥1% FVIII:C. Among all patients

Table 2: Extent of exposure to rFVIII-FS during the study for the total population (n = 631).

	Total population (n = 631)	Prophylaxis population[a] (n = 111)
Mean no. of observation days (SD)	460 (142)	n/d
Mean no. of bleeds, surgeries, and prophylactic infusions (SD) per patient per year		
Prophylactic infusions	53.1 (60.4)[b]	148.9 (49.3)
Joint bleeds	10.5 (18.0)	3.1 (8.4)
Other bleeds	4.1 (16.5)	1.9 (4.3)
Surgeries	0.1 (0.8)	0.1 (0.3)
Mean consumption (SD) per patient per year, by reason (IU/kg)		
Prophylaxis[a]	1029 (1390)	2898 (1644)
Joint bleeds	551 (1020)	189 (384)
Other bleeds	252 (1102)	109 (209)
Surgery	24 (136)	21 (134)

SD, standard deviation; n/d = not determined. [a]Defined as regular treatment ≥2 prophylactic injections per week. [b]Patients who received treatment for any prophylactic reason, not limited to the subgroup of patients who received ≥2 injections per week.

with 20–100 EDs at enrollment, two in 57 (3.5%) developed a *de novo* inhibitor (2/28 [7.1%] patients with severe disease), and among patients with >100 EDs at enrollment, *de novo* inhibitors were observed in one of 452 (0.2%) patients (1/323 [0.3%] patients with severe haemophilia). The 447 extensively pretreated patients with no present or historical inhibitor titre were observed during this study for a sum total of 572 years, yielding a rate of 1.75 inhibitor cases per 1,000 person-years of observation. Among only the 323 extensively pretreated severe haemophilia A patients, there were 409 person-years of observation, yielding a rate of 2.44 cases per 1,000 person-years.

When considering the total number of EDs accumulated by the day of first inhibitor detection, all *de novo* FVIII inhibitors except for one (2 BU/ml) were detected in patients with <150 cumulative EDs to any FVIII preparation. High-titre inhibitors were detected in two patients, one with <20 EDs and the other with <40 EDs in total on the day of first detection. The overall rate of recurrent inhibitor formation was one in 32 (3.1%) patients with a history of inhibitors. No positive inhibitor titre was detected in the study in any patient with a documented switch from plasma-derived FVIII (pdFVIII) to rFVIII-FS. However, although not documented, one cannot definitely exclude that the 27-year-old patient who experienced inhibitor recurrence during this study may have received pdFVIII at some point in the past.

Tolerability assessment

At the conclusion of the observation period, the tolerability of rFVIII-FS was globally evaluated for each patient by the physician. The tolerability of rFVIII-FS treatment was rated "very good" or "good" in 627 of 631 evaluable patients (99.4%) with available assessment data; tolerability was rated as "sufficient" for three (0.5%) patients, and for one (0.2%) patient there was no available assessment of tolerability; no patient received a rating of "insufficient tolerability". Physicians recorded patient ratings of their acceptance of the treatment during the observation period. A total of 619 of 631 evaluable patients (98.1%) rated their acceptance of the treatment as "very good" or "good." Of the remaining 12 patients, eight (1.3%) rated their acceptance as "sufficient", three (0.5%) as "insufficient", and one (0.2%) patient had no assessment available.

Discussion

This non-interventional study was designed to evaluate the safety and efficacy of full-length rFVIII-FS, as used in routine clinical practice, during a 12-month observation period in a Japanese haemophilia A patient population. With over 700 patients enrolled, this trial is one of the largest studies performed in haemophilic patients. Furthermore, the design of this Japanese study was similar to that of another large, recently completed PMS study of full-length rFVIII-FS that enrolled over 230 European patients (18). The results of both studies support the very good safety and efficacy profile of rFVIII-FS for the treatment and prevention of bleeding episodes in routine clinical practice.

On average, joint bleeding episodes in this study required 1.1 follow-up infusions of rFVIII-FS to achieve adequate haemostasis, and other (non-joint) bleeding episodes required 1.2 follow-

Table 3: Patients with positive inhibitor tests during the study (n = 7).

Inhibitor type	Patient age, years	Disease severity[a]	No. of EDs prior to enrollment	No. of cumulative EDs prior to detection	Titre at first detection (BU)	Peak level during study (BU)	Titre at end of study (BU)
De novo	1	Severe	<20	<20	16	27	27
De novo	1	Severe	<20	<40	46.1	183[b]	103.4[c]
De novo	0.1	Severe	20–100	27	2	2	1
De novo	2	Severe	20–100	100–150	1	2	2
De novo	1	Severe	>100	150–200	2	2	0
Persistent (fluctuating)	8	Severe	>100	>150	1	3	3
Recurrent	27	Severe	>100	>150	1	3	2

EDs, exposure days; BU, Bethesda units; ND, no data available. [a]Disease severity defined by baseline FVIII:C levels as follows: severe (<1%), moderately severe (1–2%), moderate (>2–5%), or mild (>5%). [b]After initiating immune tolerance therapy. [c]Titre decreased to 7.8 BU/ml on last follow-up data available after completion of study.

up infusions. The efficacy of rFVIII-FS was rated by physicians as "very good" or "good" in 99.5% of patients. No treatment with rFVIII-FS was rated "insufficient". These findings are very similar to those observed in the European study, where 85.4% of haemorrhages were controlled using one or two infusions of rFVIII-FS, and 98.7% of physicians assessed efficacy as "very good" or "good" (18). By comparison, in a recently published interim analysis of an ongoing observational study of a B-domain-deleted rFVIII product in Germany, the overall physician assessment of efficacy was "very good" or "good" in 77.0% of treated cases (19).

When considering the extent of rFVIII-FS exposure, an average of 6,066 (± 6,583) IU were administered per patient per month in the current study (including patients on prophylaxis). Interestingly, patients in the European observational study consumed more than twice the amount of FVIII (mean 14,000 IU per patient per month) (18). The comparatively lower rFVIII consumption in this Japanese study may be related to the slightly smaller proportion of severe and moderately severe haemophilia A patients (<2% FVIII:C) enrolled (80.0% of patients) compared to 99.5% of patients in the European rFVIII-FS surveillance studies. The disparity between consumption rates may also be indicative of differences in body weight, culture, and/or medical practices between Japan and Europe, which would emphasize the importance of performing confirmatory studies in a Japanese patient population.

In the safety evaluation, seven cases of FVIII inhibitor formation accounted for all AEs considered related to treatment (by definition, inhibitors were to be considered drug-related). Because they interfere with the haemostatic efficacy of infused FVIII, inhibitor development is a serious concern for the management of patients with haemophilia. The risk of inhibitor formation is related to numerous endogenous factors (e.g. FVIII gene mutation, severity of haemophilia) and exogenous factors (e.g. intensity of treatment, surgeries, on-demand treatment versus prophylaxis) (20, 21). The risk for inhibitor development decreases with additional exposure to infused FVIII; therefore young patients with a limited number of previous EDs are at highest risk. In this study, the rate of *de novo* inhibitor formation in high-risk patients (<20 previous EDs at enrollment) was 2/62 (3.2%). This figure compares favourably to the rate reported in the European observational study (2/25; 8.0%) (18), although the difference in the incidence rates may be related to the greater number of mild and moderate haemophilia patients included in the Japanese cohort, as these patients are at lower risk compared to severe haemophiliacs. In the subgroup of only severe haemophilia A patients at high risk in our study, the inhibitor rate was 5.7% (2/35). The findings of both these PMS studies are supportive of the inhibitor incidence reported in a phase III clinical trial with rFVIII-FS in PUPs and MTPs with severe haemophilia A (9/60; 15%) (5). Because the incidence of inhibitor development among previously untreated severe patients is generally considered to be in the range of 20%-30% (10), these findings suggest that full-length rFVIII-FS has a low incidence of inhibitor formation in these patients. Moreover, reports of patients with positive inhibitor tests suggest a positive correlation between the number of EDs prior to and after enrollment before the onset of inhibitor development.

In contrast to high inhibitor risk patients, PTPs (those with at least 100 or 150 EDs to infused FVIII), are generally considered to be at low risk for inhibitor formation. This makes pretreated patients the ideal population in which to assess the immunogenicity of new FVIII products (11, 22). In the Japanese cohort studied here, the rate of *de novo* inhibitor formation in patients with >100 EDs at enrollment was 0.21% (1/477), which is consistent with reported rates in the European observational study (0/181, or 0%) (18) and a phase III study of patients with >150 previous EDs at enrollment (0/71, or 0%) (3). Notably, there were no reports of inhibitor formation in patients with a documented switch from a pdFVIII concentrate as a previous therapy to rFVIII-FS in this study. A retrospective study of a cohort of 838 PTPs with haemophilia A in the US determined an incidence of 2.14 inhibitor cases per 1,000 person-years assessed (2.26 cases per 1,000 person-years among only those with severe disease) (23). In our population of extensively pretreated (>100 EDs at enrollment) Japanese patients with no evidence of prior or current inhibitor, we calculated a rate of 1.75 inhibitor cases per 1,000 person-years of observation (2.44 cases per 1,000 person-years among only those with severe disease). Although these rates appear comparable, the US report excludes patients without a confirmation inhibitor test, which was not done in our observational study. One would expect this methodological difference to bias the incidence rates in the Japanese study higher relative to that of the US study. Collectively, the inhibitor safety findings in our study suggest that rFVIII-FS may have a low immunogenic potential.

There are a number of caveats to the interpretation of inhibitor incidence within the context of a surveillance study such as the one described here. One is that FVIII genotyping could not be specified within the design of the study; therefore, the proportion of high inhibitor risk (e.g. large deletion) compared to low inhibitor risk (e.g. single nucleotide substitution) subjects who were included in the analyses is not known. Two, the frequency of inhibitor testing also could not be specified by study protocol. Since in normal clinical practice routine inhibitor testing may only occur once or twice annually, unless an inhibitor is suspected, it must be considered that transient inhibitors and low-titer inhibitors that do not have a clinical impact may be missed. This would lead to a lower inhibitor incidence in a surveillance study compared to an interventional trial. Third, the lack of centralised inhibitor testing during this study leaves open the possibility for variation in the quality of testing performed at individual centres that may either lead to false positive or, more critically, false negative results that could depress the determined incidence. For these reasons, surveillance studies are best compared to other non-interventional, observational trials, and the comparability of the findings in our study to those of the large epidemiological study in the US (23) described above, suggests that the results are valid when such caveats are taken into consideration. Surveillance studies do, however, provide critical insight into the use of a product within the usual practice setting. The surveillance study described here would be expected to identify the occurrence of clinically relevant inhibitors (i.e. inhibitors that would require medical intervention) within the Japanese haemophilia population studied, and therefore would be of relevance to treating physicians.

In this study, there was no indication of blood-borne pathogen transmission from use of rFVIII-FS, which was a concern for plasma-derived concentrates in the past (24–28). Patients rated their own acceptance of rFVIII-FS treatment as "very good" or "good" in 98.1% of cases, indicating that the therapy was well tolerated.

In summary, this observational PMS study demonstrates a very good efficacy, safety, and tolerability profile for rFVIII-FS in a large population of Japanese patients with mild to severe haemophilia A, with no indication of pathogen transmission and a low rate of inhibitor formation. These results confirm those obtained in a similar European observational study of rFVIII-FS. Together, the results of these observational trials add substantial additional evidence of the safety, tolerability, and efficacy to the profile of rFVIII-FS determined in pre-licensure studies.

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Safety and efficacy of sucrose-formulated full-length recombinant factor VIII: Experience in the standard clinical setting

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Summary

The safety of full-length sucrose-formulated recombinant factor VIII (rFVIII-FS; Kogenate® FS) for up to 24 months of use was evaluated in a postmarketing observational study in Europe. Long-term safety and efficacy data were available for 212 patients with severe haemophilia A, including 13 previously untreated patients (PUPs) and 12 patients with 1–19 exposure days (EDs). Patients accumulated a mean (± SD) of 187 (121) EDs to rFVIII-FS and received a total of 39,627 infusions, mainly for prophylaxis and for the treatment of 4,283 spontaneous or trauma-related bleeds during an average observation time of 710 (136) days. Of these bleeding episodes, 85.4% were successfully treated with one or two infusions of rFVIII-FS. Haemostasis was also evaluated during 46 minor to major surgical procedures, and the response to infusion was "excellent" or "good" in all cases. FVIII inhibitor formation was observed in six patients (two *de novo*; four persistent or recurrent). The *de novo* cases represent 8.0% (2 of 25) of patients who reported 0–19 previous EDs at study entry. Four of the five patients who reported possible drug-related adverse effects developed inhibitors. The results of this observational study demonstrate the efficacy and safety of rFVIII-FS during normal clinical use in the treatment of patients with severe haemophilia A. Furthermore, these findings are consistent with those of previous phase III clinical studies with rFVIII-FS, particularly with regard to its efficacy and low incidence of inhibitor formation.

Keywords

Haemophilia, recombinant factor VIII, Kogenate, inhibitors, prophylaxis

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Introduction

Factor VIII (FVIII) replacement therapy for haemophilia A once relied solely on clotting factor concentrated or purified from the plasma cryoprecipitate of donor blood (1). The advent of FVIII production via recombinant DNA technology was a milestone in haemophilia treatment because FVIII concentrate became more widely available, reducing the need for human plasma-derived products that may carry a risk for transmission of blood-borne infections. Recombinant FVIII-FS (rFVIII-FS; Kogenate® FS in North America; KOGENATE® Bayer in Europe; Bayer HealthCare Pharmaceuticals) is a full-length rFVIII product formulated with sucrose, instead of human albumin, as a stabilizer. The production process for rFVIII-FS was designed to eliminate human-derived proteins from the final formulation and purification steps of the product and to reduce the likelihood of pathogen transmission (2). Clinical studies to date have reported no pathogen transmission with rFVIII-FS (3–7).

Evaluation of rFVIII-FS in several clinical studies showed a positive safety and efficacy profile. In clinical studies involving previously treated patients (PTPs; n = 71) and previously untreated or minimally treated patients (PUPs/MTPs; n = 61) from

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North America and Europe (3, 4), bleeding episodes were successfully treated with one or two infusions of rFVIII-FS in 80.5% (5) and 89% (6) of cases. Moreover, less than 1% of infusions were associated with adverse events (AEs) that were considered possibly drug related. In addition, the efficacy and safety of rFVIII-FS have been evaluated for use during a total of 37 surgical procedures in clinical studies, including its administration by continuous infusion (7, 8). In all cases, haemostatic outcomes for patients receiving rFVIII-FS during surgery were rated "good" or "excellent." Overall, rFVIII-FS has been well tolerated and effective in controlling bleeding in patients with severe haemophilia A in the clinical setting.

The formation of inhibitory antibodies to FVIII is a potentially serious complication of haemophilia A treatment. Patients at increased risk of inhibitor formation are those who suffer from severe disease (9), have certain genetic mutations in the FVIII gene (10) or possess variants in specific genes that constitute the major histocompatibility complex (11, 12) or are involved in immune response (e.g. interleukin [IL]-10) (13), are PUPs or MTPs, or are of African-American or Hispanic ethnicity (14). Inhibitors occur in approximately 20%–30% of PUPs and in 1%–3% of PTPs treated with other recombinant FVIII products (15–17). Phase III clinical trials on rFVIII-FS reported no *de novo* inhibitor formation in PTPs and inhibitors occurring in 15% of PUPs/MTPs (4). Here we report the results of a post-licensure observational study designed to evaluate the safety and efficacy of rFVIII-FS as used in clinical practice for up to 24 months in a large (>200 patients), unselected haemophilia A patient population.

Materials and methods

Patient selection

The study enrolled males with severe haemophilia A (<2% FVIII:C at baseline) of any age. There were no restrictions in enrolling patients with additional underlying diseases or chronic infections, aside from the contraindications for Kogenate® FS – i.e. known intolerance, allergy, or hypersensitivity to mouse or hamster proteins or other constituents of the preparation (Bayer HealthCare Pharmaceuticals, Berkeley, CA, USA).

Ethical conduct and confidentiality

The study protocol was approved by the appropriate ethics committees as required by local law in Denmark, Italy, Spain, and Sweden; this was not required in the other participating countries (Austria, Belgium, France, Greece, Netherlands, and Switzerland).

The study was carried out in accordance with the approved SmPC (Summary of Product Characteristics), EMEA (European Agency for the Evaluation of Medical Products) guidelines, and applicable local laws and regulations.

Only data collected during regular therapy was documented; no intervention into the investigators' decisions were required or performed, and no additional diagnostic or monitoring procedures were to be applied. Therefore, the patients' informed consent was not necessary. All records were kept confidential; only patient number, initials, and date of birth, but not patient names, were supplied to the sponsor.

Study design

This study was designed as a prospective, open-label, multinational (all-European) postmarketing surveillance study to collect safety and efficacy data over a 24-month period for rFVIII-FS used to treat patients with severe haemophilia A in a clinical setting or in home therapy. During the observation period, patients were treated solely with rFVIII-FS for prophylaxis and for on-demand treatment of spontaneous bleeding, trauma-related bleeding, surgery, or immune tolerance induction (ITI). Regular prophylaxis was defined as ≥2 prophylactic infusions per week for ≥80% of the observation time. The treatment dose and regimen were decided by the treating physician. Data were collected in case report forms, which included data obtained from patient treatment diaries (infusion reports).

The efficacy analysis was based on observations documented in the case report forms (number of infusions with dosage, reason for infusion, bleeding site, and assessment of response) and on a general efficacy assessment performed by the attending physician at the end of the observation period. The safety analysis comprised FVIII recovery data, inhibitor assay results, maintenance of haemostasis during surgery, laboratory examinations, and AEs recorded during the observation period as well as a drug tolerability assessment by the physician at the end of the study period. An AE was defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure (18). An AE that resulted in any of the following was considered a serious AE (SAE): death, life-threatening condition, hospitalization or prolongation of existing hospitalization, or persistent or significant disability/incapacity. An AE was classified as an adverse drug reaction (ADR; or serious ADR, if appropriate) if considered by the physician to be possibly related to the study drug or its administration (19).

Data analysis

At the end of the observation period, the efficacy of the therapy was evaluated globally for each patient by the physician; the biometric evaluation was primarily descriptive and exploratory, using summary statistics for categorical and quantitative data. Patients who received at least one infusion were included in the analysis; patients with missing data were presented as a separate category. Percentages were calculated as a proportion of each category, including the category for missing values. In some subgroup analyses, percentages were calculated based on available figures (adjusted frequencies).

The incidence rates of adverse events and drug reactions were calculated and defined as the number of events divided by the number of patients at risk, where number of events equals the number of patients reporting the event and the number at risk equals all patients valid for safety analyses.

Results

Patients

A total of 231 male patients from 54 haemophilia treatment centres in ten European countries were enrolled and observed in the study from December 3, 2002, through December 31, 2005;

Table 1: Patient baseline characteristics and demographics (N = 220).

Patient characteristics	N	%
Total population	220	100
Age, years		
<2	14	6.4
2 to <12	54	24.5
≥12 to <18	24	10.9
≥18	128	58.2
Ethnicity		
White	180	81.8
Black	3	1.4
Asian	2	0.9
Other	8	3.6
Not reported	27	12.3
Factor VIII:C		
<1%	197	89.5
1%–2%	22	10
>2%	1	0.4
History of haemophilia		
Familial (inherited)	129	58.6
New mutation	57	25.9
Not known	34	15.5
EDs prior to trial		
Previously untreated	13	5.9
1–19	12	5.5
20–100	14	6.4
>100	181	82.3
History of inhibitors		
Positive history (total)	33	15.0
≥5 BU	20	9.1
<5 BU	11	5.0
Titre not available	2	0.9
Seropositive status		
HIV	43	19.5
Hepatitis A	112	50.9
Hepatitis B	179	81.4
Hepatitis C	116	52.7
Patients with target joints	84	38.2

BU, Bethesda units; EDs, exposure days; HIV, human immunodeficiency virus.

however, 11 patients either received no infusions (n = 6) or were lost to follow-up (n = 5). Thus, 220 eligible patients (mean age, 23.6 years; range, <0.1–71 years) were included in the analysis. FVIII activity was <1% in 197 (89.5%) patients, 1%–2% in 22 (10.0%) patients, and >2% in 1 (0.5%) patient. A target joint was specified for 84 (38.2%) patients, and the most frequently affected joint was the knee (n = 27). Infusion reports were available for 212 (96.4%) patients, and 210 (95.5%) patients had reports that detailed all infusions.

Most of the patients with available infusion data (n = 181, 82.3%) had been heavily treated in the past, with >100 previous exposure days (EDs) accumulated before study entry. Another 14 (6.4%) patients had 20–100 previous EDs, 12 (5.5%) had 1–19 EDs, and 13 (5.9%) were previously untreated patients (PUPs). Of the 207 previously exposed patients, 108 (52.2%) patients had previously been treated with one or more recombinant FVIII products and 92 (44.4%) with a plasma-derived FVIII product; the remaining seven (3.4%) patients received either an alternate, non-FVIII product or an unknown product. Of the 108 patients who had previously received recombinant FVIII, 42 (38.9%) had used human albumin-stabilized Kogenate® (Bayer HealthCare), the predecessor product of the sucrose-stabilized KOGENATE® Bayer (Bayer HealthCare).

A history of inhibitors to FVIII was reported in 33 (15.0%) patients enrolled in the study. Table 1 summarizes the baseline characteristics and demographics of the study population.

Infusion and consumption summary

Patients were observed over a mean (± SD) of 710 (± 136) days, during which they accumulated a mean of 187 (± 121) EDs. Observation times ≥1 year were achieved for 214 (97.3%) patients. A total of 39,627 infusions were administered to 212 patients with available infusion reports, with a mean of 188 (± 121) infusions per patient. Patients were infused with rFVIII-FS for prophylaxis, spontaneous bleeds, trauma-related bleeds, ITI therapy, surgery, or other reasons (Table 2). The overall mean infusion dose was 31.4 (± 14.9) IU/kg for all patients excluding those who received ITI therapy. A higher mean dose was administered to patients undergoing surgery (52.2 [± 28.6] IU/kg) or ITI therapy (90.5 [± 21] IU/kg). The mean dose for prophylactic infusion was 29.5 (± 14.5) IU/kg, slightly lower than that administered for the treatment of trauma-related bleeding (33.9 [± 15.8] IU/kg) or spontaneous bleeding (33.3 [± 15.6] IU/kg).

On average, each patient received a mean of 147,000 (± 122,000) IU rFVIII yearly (median 118,000 IU, range 2,000–744,000 IU). Median consumption for patients with complete data was 4,400 IU/kg/year in the prophylaxis group and 1,600 IU/kg/year in the non-prophylaxis group. Patients who received ITI (n = 8) had higher factor utilization (634,000 [± 1,106,000] IU per patient per year). Excluding patients undergoing ITI, the mean consumption for patients with at least 50 weeks of data was 4,600 (± 2,100) IU/kg/year in the prophylaxis group (n = 68) and 2,000 (± 1,500) IU/kg/year in the non-prophylaxis group (n = 130).

Bleeding events

During the study, a total of 4,283 bleeding events were documented in patients for whom infusion reports were available (n = 210). Of these, 138 patients reported 2,487 spontaneous bleeds, and 156 patients experienced 1,796 bleeds related to trauma (Table 3). The most commonly reported bleeding sites were the joints (71.9%); other bleeding sites included muscle (15.2%), head (6.3%), internal organs (1.1%), and other sites (5.9%). A total of 33 (15.7%) patients reported no bleeding events during the course of the study, including six of 70 (8.6%) patients re-

Table 2: Infusion summary (n = 212).

Total no. of infusions	39,627
Mean (± SD) infusions per patient	188 (121)
No. of infusions by reason, n (%)	
Prophylaxis	28,896 (72.9)
Spontaneous bleeding	4,048 (10.2)
Trauma-related bleeding	3,334 (8.4)
ITI	2,062 (5.2)
Surgery	487 (1.2)
Missing or other	800 (2.0)
Mean (± SD) infusion dose by reason, IU/kg	
All patients (excluding ITI)	31.4 (14.9)
ITI	90.5 (21.0)
Surgery	52.2 (28.6)
Trauma-related bleeding	33.9 (15.8)
Spontaneous bleeding	33.3 (15.6)
Prophylaxis	29.5 (14.5)
Other	33.3 (13.5)
No. of patients on regular prophylaxis[a] (%)	70 (31.8)
No. of infusions for patients on regular prophylaxis	21,340
No. of infusions by reason for patients on regular prophylaxis, n (%)	
Prophylaxis	19,732 (92.5)
Trauma-related bleeding	705 (3.3)
Spontaneous bleeding	563 (2.6)
Surgery	181 (0.8)
Missing or other	159 (0.7)

ITI, immune tolerance induction; SD, standard deviation. [a]Includes only patients who received ≥ 2 infusions for prophylaxis per week for ≥ 80% of the study period (not for ITI).

Table 3: Bleeding summary (n = 210).

No. of patients with bleeds, n (%)	
Total	177 (84.3)
Spontaneous bleeds	138 (65.7)
Trauma-related bleeds	156 (74.3)
No. of bleeds, n (%)	
Total	4,283 (100)
Spontaneous bleeds	2,487 (58.1)
Trauma-related bleeds	1,796 (41.9)
Mean (± SD) no. of bleeds per patient per year (n = 204)[a]	
All bleeds	10.4 (13.6)
Spontaneous bleeds	6.1 (10.5)
Trauma-related bleeds	4.3 (7.1)
Mean (± SD) no. of infusions for bleeds per patient per month	
All bleeds	1.51 (1.78)
Spontaneous bleeds	0.80 (1.29)
Trauma-related bleeds	0.71 (1.11)
No. of bleeds for patients on regular prophylaxis (n = 68), n (%)	
All bleeds	656 (100)
Spontaneous bleeds	294 (44.8)
Trauma-related bleeds	362 (55.2)
Mean (± SD) no. of bleeds per patient on regular prophylaxis per year (n = 68)[a]	
All bleeds	4.8 (5.0)
Spontaneous bleeds	2.2 (3.6)
Trauma-related bleeds	2.6 (3.6)
Mean (± SD) no. of infusions for bleeds per patient on regular prophylaxis per month	
All bleeds	0.75 (0.84)
Spontaneous bleeds	0.34 (0.65)
Trauma-related bleeds	0.41 (0.59)

SD, standard deviation. [a]For patients with ≥ 350 observation days on the study.

ceiving regular prophylaxis therapy. In patients who had ≥350 observation days on the study (n = 204), a mean of 10.4 (± 13.6) bleeds per year was reported overall. The mean number of bleeds per patient per month was 0.9 (± 1.1) (range, 0–6.2 bleeds) for patients with detailed infusion reports.

For patients receiving regular prophylaxis, 294 spontaneous bleeds and 362 trauma-related bleeds were documented. A mean of 4.8 (± 5.0) bleeds per year was reported for those with ≥ 350 observation days on a regular prophylaxis regimen during the study (n = 68). In contrast, all other non-ITI, non-prophylaxis patients (n = 132) reported a mean of 1.16 (± 1.29) bleeds per month, which corresponds to a mean of 13.9 bleeds per year during the observation period. The latter patient group includes on-demand patients and those on irregular prophylaxis regimens.

The majority of bleeding episodes (n = 3,658, 85.4%) were successfully treated with one or two infusions of rFVIII-FS. Overall, responses to rFVIII-FS treatment were rated by physicians as "very good" or "good" in 217 of 220 study subjects (98.6%) who were treated with rFVIII-FS in the study.

Surgical procedures

During the study, 37 patients underwent 46 minor or major surgical procedures, including 17 knee replacements or synovectomies; nine tooth extractions or dental implantations; six orthopedic surgeries involving the hip, ankle, elbow, spine, or Achilles tendon; six replacements, implantations, or removals of intravenous access devices; four skin biopsies or cyst ablations; two abdominal surgeries; one eye atheroma resection; and one cholecystectomy. Surgery accounted for 1.2% of all infusions administered during the study period, with a mean dose of 52.2 IU/kg (± 28.6) per infusion per patient. Haemostasis was assessed by study investigators as "excellent" in 28 cases or "good" in 16 cases. None of the patients who underwent surgery developed inhibitors.

Safety evaluation

All 220 patients were included in the safety analysis. Seventy (31.8%) patients reported 130 AEs, and 45 (20.5%) patients reported 72 SAEs. Of these, only 11 AEs that occurred in five (2.3%) patients were considered by physicians to be possibly related to the study drug or its administration (ADRs), which included eight events reported by four patients that were considered serious (SADRs) (Table 4). Four of these eight SADRs were related to inhibitor formation.

Four deaths occurred during the study. The causes of death were non-Hodgkin's lymphoma (n = 2) and intracranial haemorrhage (n = 2), neither of which was considered related to the study drug. For the study population overall, physicians considered the safety of rFVIII-FS to be "very good" or "good" in 99.1% of the cases treated.

Type of event	ADRs (n = 5)		SADRs (n = 4)	
	No. of patients[a]	No. of events	No. of patients[a]	No. of events
Factor VIII inhibition	4	5	3	4
Catheter placement complications	1	1	1	1
Haemarthrosis	1	3	1	3
Pain in extremity	1	1	0	0
Arthralgia	1	1	0	0
Total number of events		11		8

ADRs, adverse drug reactions; SADRs, serious adverse drug reactions. [a]Each patient may have experienced more than one type of event.

Table 4: Frequency of adverse drug reactions (ADRs) and serious adverse drug reactions (SADRs).

Table 5: Patients with positive inhibitor titres during the study (n = 6).

	Before study		During study				
Age, years	No. of EDs prior to study	Last titre (BU)	First titre (BU)	Peak titre (BU)	Last titre (BU)	Inhibitor description	Treatment notes
De novo inhibitors							
1	0	Negative	20.0[a]	272.0	108.0	*De novo*	rFVIII-FS discontinued
1	1–19	Negative	2.2[b]	2.2	Negative	*De novo*	Successful ITI
Recurrent or preexisting inhibitors							
2	1–19	2.0	2.0	2.0	2.0	Persistent low titre	NA
7	20–100	Missing	5.7	7.4	Negative	Recurrent[c]	NA
6	>100	11.0	13.6	13.6	3.0	Preexisting	Decreasing titre during ITI treatment
18	>100	1.5	154.0	315.0	250.0	Increase at start of ITI	rFVIII-FS discontinued

BU, Bechesda units; EDs, exposure days; ITI, immune tolerance induction; NA, not available. [a]*De novo* inhibitors detected after 15 ED, [b]*De novo* inhibitors detected after 9 ED. [c]Positive history of inhibitor.

Nine (4.1%) patients seroconverted from negative to positive after vaccination for hepatitis A or B during the study. There were no conversions for hepatitis C reported during the study.

Inhibitor formation

During the observation period, FVIII inhibitor assays were conducted in 175 (79.5%) patients. Between one and 20 inhibitor assays were conducted in each of these patients. Six patients (age range, 1–18 years) were found to have a positive inhibitor test during the course of the study, including three patients who had positive titres at the start of the study and one patient who had a positive inhibitor history but did not have a documented titre at the start of the observation period (Table 5). Of the six patients with inhibitors, two entered the study with >100 EDs, one with 20–100 EDs, two with 1–19 EDs, and one patient was previously untreated.

The six patients who presented with inhibitors during the study period included two cases of *de novo* inhibitors. The incidence of *de novo* inhibitors was 1/13 (7.7%, high-titre) in PUPs and 1/12 (8.3%, low-titre) in patients with 1–19 EDs prior to study entry. No *de novo* inhibitor was detected in patients with at least 20 previous treatments with FVIII (n = 195). Of the two patients with *de novo* inhibitors, the high-titre patient discontinued rFVIII-FS therapy altogether and the low-titre patient underwent successful ITI treatment. In addition, the latter patient reported a recurrent episode of the inhibitor (1 BU) six months after resolution of the initial episode.

In the three patients who had documented positive titres for inhibitors at the start of the study, the titre remained unchanged for one patient who did not receive ITI (2.0 BU), decreased from 13.6 BU to 3.0 BU for one patient who underwent ITI, and surged to a peak of 315.0 BU for one patient who initiated ITI (Table 5). The latter patient discontinued rFVIII-FS therapy altogether. The fourth patient, who had a history of inhibitors but no documented inhibitor test at study entry, developed inhibitor titres of 5.7 BU and 7.4 BU during the study, and eventually converted to negative by the end of the study. This patient was the only one of 33 patients with a history of inhibitors who developed a recurrent inhibitor after switching to rFVIII-FS from another product (he had previously received a B-domain–deleted [BDD] product).

Of the patients who underwent surgical procedures with intensive treatment during the study, four had a prior history of inhibitor formation. None of these patients developed inhibitors during surgery.

Discussion

Recombinant FVIII formulated with sucrose (rFVIII-FS) has been available for the treatment of haemophilia A since 2000. The pres-