# 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, Bethesda 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-

ent study, a 24-month-long, multinational, postmarketing surveillance study, was designed to evaluate the safety and efficacy of rFVIII-FS during its use in the clinical and home therapy settings.

The results of this study are consistent with the results of the pre-licensure clinical trials and indicate that rFVIII-FS is well tolerated and efficacious for the treatment and prevention of bleeding episodes. There were no reports of pathogen transmission during the study. The final assessment by the physicians of the efficacy of rFVIII-FS was "very good" or "good" in 98.7% of the cases treated. The efficacy results of this study are comparable to those obtained from the licensure clinical trials in terms of the mean number of bleeds per patient per month for patients on prophylaxis (0.4 in this study vs. 0.64 in an international study of PTPs) and the percentage of bleeding episodes successfully treated with one or two infusions (85.4% in this study vs. 93.5% and 89.0% in an international study of PTPs and a study of PUPs/MTPs, respectively) (3, 4). A recently published postmarketing surveillance study of a BDD rFVIII product observed 217 patients with mild to severe hemophilia A who were treated for a mean of 24.7 months in treatment centres in Germany (20). Although differences in study design and definitions make it difficult to compare between studies, in the BDD rFVIII postmarketing surveillance study the final overall physician assessment of efficacy was "very good" or "good" in 77.0% of cases treated.

The development of inhibitors against replacement FVIII is a major concern associated with the treatment of haemophilia A. Factors such as particular FVIII gene mutations, particular genetic features, racial background, familial history, limited prior exposure to FVIII products, and even variations in the FVIII manufacturing process have all been implicated as potential risk factors that can influence inhibitor development in patients (10, 21–23). Clinical studies of other rFVIII products in PUPs have documented *de novo* inhibitor rates of about 30% (24). In contrast, a recent phase III clinical study of rFVIII-FS in PUPs and MTPs (≤4 EDs prior to study) found a lower rate of *de novo* inhibitor formation (9/60, or 15.0%) (4). The rate of *de novo* inhibitor formation in high-risk patients (<20 EDs at study entry) that was documented in this postmarketing surveillance study was 8.0% (2/25), and 7.7% (1/13) in PUPs.

Phase III evaluation of rFVIII-FS in PTPs with ≥100 EDs at study entry showed no *de novo* inhibitor formation among 71 patients studied (5). In the current observational study, *de novo* inhibitors were reported in 0.5% (1/207) of patients with ≥ 1 ED prior to entry. While inhibitor assays were performed in only 175/220 (79%) of all patients, this low incidence of *de novo* inhibitors may indicate a relatively low immunogenic potential for rFVIII-FS in PTPs, if confirmed in larger studies.

Because postmarketing surveillance studies evaluate "real-world" use of FVIII, inhibitor assays are not performed as frequently as in clinical studies. Thus, occurrences of transient or low-titre inhibitors without clinical relevance might be missed in these types of studies. Nonetheless, the rate of *de novo* inhibitors found in this study of rFVIII-FS is low and consistent with the rates observed in the rFVIII-FS phase III program.

In summary, this observational study has found that the use of rFVIII-FS in the normal clinical setting was safe and well tolerated, with no clinical or laboratory evidence of pathogen transmission, and a low rate of inhibitor formation. Furthermore, rFVIII-FS was shown to be efficacious for the treatment of bleeding episodes and for haemostatic control during surgical procedures. This observational study provides safety and efficacy data on "real-world" use of rFVIII-FS, with no restrictions on patient enrollment and obtained data, which support the results of the rFVIII-FS clinical study program.

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