Prospective surveillance study of haemophilia A patients switching from moroctocog alfa or other factor VIII products to moroctocog alfa albumin-free cell culture (AF-CC) in usual care settings

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Summary

This prospective, open-label, postauthorisation safety surveillance study assessed clinically significant inhibitor development in patients with severe haemophilia A transitioning from moroctocog alfa or other factor VIII (FVIII) replacement products to reformulated moroctocog alfa (AF-CC). Males aged ≥ 12 years with severe haemophilia A (FVIII:C) < 1 IU/dl), > 150 exposure days (EDs) to recombinant or plasma-derived FVIII products, and no detectable inhibitor at screening were enrolled. Primary end point was the incidence of clinically significant FVIII inhibitor development. Secondary end points included annualised bleeding rate (ABR), less-than-expected therapeutic effect (LETE), and FVIII recovery. Patients were assigned to one of two cohorts based on whether they were transitioning to moroctocog alfa (AF-CC) from moroctocog alfa (cohort 1; n=146) or from another recombinant or plasma-derived FVIII product (cohort 2; n=62). Mean number of EDs on study was 94 (range, 1–139). Six positive FVIII in-

hibitor results, as determined by local laboratories, were reported in four patients; none were confirmed by a central laboratory, no inhibitor-related clinical manifestations were reported, and all anti-FVIII antibody assays were negative. Median ABRs were 23.4 and 3.4 in patients categorised at baseline as following on-demand and prophylactic regimens, respectively; 86.5 % of bleeding episodes resolved after one infusion. LETE incidence was 0.06 % and 0.19 % in the on-demand and prophylaxis settings, respectively. FVIII recovery remained constant throughout the study. No new safety concerns were identified. This study found no increased risk of clinically significant FVIII inhibitor development in patients transitioning from moroctocog alfa or other FVIII replacement products to moroctocog alfa (AF-CC).

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Introduction

The mainstay of treatment for patients with haemophilia A is to attain haemostasis by replacing the factor VIII (FVIII) deficiency with specific factor replacement therapy, either on-demand to treat bleeding events as they occur or as prophylaxis to reduce the number of spontaneous bleeding events (1–3). Although inclusion of viral inactivation steps in the manufacturing process reduced the infectious disease risk with plasma-derived concentrates, concern lingered regarding the transmission of resistant viruses and prions (4–8). With the introduction of recombinant DNA-derived clotting factors, the infectious disease risk that complicated the use of plasma-derived replacement factors has been virtually eliminated. Safety improvements over successive generations of recombi-

nant FVIII (rFVIII) products resulted in the removal of all exogenous animal and human proteins from the final formulations and cell culture mediums of third-generation replacement products (9).

Despite the enhanced safety of currently available FVIII replacement products, one of the most serious complications that can occur with their use is the development of inhibitors to FVIII. Inhibitors are antibodies that neutralise FVIII activity (FVIII:C) and render the use of even large amounts of FVIII replacement products ineffective. Inhibitors develop in about 30 % of previously untreated patients with severe haemophilia A (10, 11), and at a rate of three per 1,000 person-years in previously treated patients (12). The majority of inhibitor development in haemophilia A occurs soon after the initial exposure to FVIII replacement, with a

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median time to onset of inhibitor formation of 13-15 exposure days (EDs) (13–15). Patients with inhibitors experience more life-threatening bleeding complications, greater disability, and lower life expectancy, require more complicated treatment, and incur higher treatment costs than haemophilia patients without inhibitors (16–21). Low-titre inhibitors (≤5 BU) in patients are typically treated with increased doses of FVIII replacement, with the objective of saturating the inhibitor and establishing haemostatic levels of the missing coagulation factor. For haemophilia patients with high-titre inhibitors (>5 BU) and for those with low-titre inhibitors in whom it is not possible to achieve haemostasis using FVIII replacement therapy, the current standard of care includes treatment with recombinant coagulation factor VIIa or activated prothrombin complex concentrates (22). The influence of the type of FVIII replacement product used on inhibitor development remains controversial; however, clinicians are often reluctant to switch between FVIII products because of a concern of exposing the patient to neoantigens and triggering the development of inhibitors (23, 24).

Moroctocog alfa (albumin-free cell culture; AF-CC) (ReFacto AF; Wyeth Pharmaceuticals, Inc. [Pfizer], Philadelphia, PA, USA) is indicated for the treatment and prophylaxis of bleeding in adults and children with haemophilia A (25). It is produced using a modification of the previous process used to manufacture moroctocog alfa (ReFacto°; Wyeth Pharmaceuticals, Inc. [Pfizer], Philadelphia, PA, USA) that eliminated the addition of all human– and animal–derived proteins and includes a virus-retaining nanofiltration step during purification, thereby eliminating the potential risk of viral contamination (26). Two clinical studies reported by Recht et al. (27) confirmed that the risk of developing inhibitors to FVIII following the administration of moroctocog alfa (AF-CC) is comparable to that observed with its predecessor, moroctocog alfa.

This study was conducted to fulfil a European Medicines Agency (EMA) requirement for postauthorisation safety surveillance and risk management and to ensure that moroctocog alfa (AF-CC) had an acceptable rate of inhibitor development. The primary objective was to assess safety, particularly with regard to clinically significant inhibitor development, in patients with severe haemophilia A who were transitioning from moroctocog alfa or other FVIII replacement products to moroctocog alfa (AF-CC) in usual care settings.

Materials and methods

Patients

The study included male patients ≥12 years of age with severe haemophilia A (FVIII:C<1 IU/dl) who had received treatment with moroctocog alfa or other recombinant or plasma-derived FVIII replacement products for >150 exposure days (EDs) and had no detectable inhibitor at screening (any measured Bethesda inhibitor titre ≥0.6 BU, regardless of the laboratory normal range, or any Bethesda inhibitor titre higher than the upper limit of normal for the testing laboratory at the time of screening). Patients with a personal history of FVIII inhibitors were eligible for inclusion. Key ex-

clusion criteria included the presence of any additional bleeding disorder, treatment with immunomodulatory therapy (including immune tolerance induction) during the screening period, known hypersensitivity to hamster protein, or prior exposure to moroctocog alfa (AF-CC).

Study design

This was a prospective, interventional, open-label study that evaluated the overall safety of moroctocog alfa (AF-CC) in patients transitioning from moroctocog alfa or other FVIII replacement products to moroctocog alfa (AF-CC) in usual care settings. Patients were asked to participate in the study in a nonconsecutive manner at the discretion of the study investigators. The study was conducted from May 2009 to March 2013 at 73 centres in Austria, Belgium, Denmark, Finland, France, Germany, Greece, Hungary, Italy, The Netherlands, Romania, Spain, Sweden, and the United Kingdom (see Appendix, available online at www.thrombosis-online.com). This study was conducted in compliance with Good Clinical Practice guidelines and in accordance with the principles of the Declaration of Helsinki. The protocol was approved by an independent review board or ethics committee at each participating centre, and all patients or their legal guardians provided written informed consent prior to participation. The study is registered at ClinicalTrials.gov (NCT00884390).

Enrolled patients were assigned to one of two cohorts based on prior therapy: cohort 1 included patients who switched from moroctocog alfa to moroctocog alfa (AF-CC) and cohort 2 included those who switched from any other recombinant or plasma-derived FVIII product to moroctocog alfa (AF-CC). Moroctocog alfa (AF-CC) was administered as a short intravenous infusion, with the dose and frequency of administration prescribed by the treating physician according to local standard of care and in accordance with the local approved prescribing information (25). Patients maintained a paper infusion log that could be used to track EDs, reason for infusion (on demand, preventive, or prophylaxis), and assessments of on–demand infusions given to treat bleeding episodes. Preventive therapy was defined as FVIII replacement therapy given before an event that could increase the risk of bleeding (e.g. surgery or exercise). Study visits were based on ED milestones (ED 1, after 10–15 EDs, and after 50 EDs) to monitor the development of FVIII inhibitors, as well as time-based visits at six-month intervals. Patients who reached six months without accruing 10–15 or 50 EDs underwent the six-month interval visit. The final visit occurred after 100 EDs were reached. A follow-up telephone call was conducted at least 28 days after the final visit to collect information on adverse events (AEs) and concomitant medications.

Laboratory assessments for the presence of FVIII inhibitors were conducted at screening (while still receiving prior FVIII therapy, before switching to moroctocog alfa [AF-CC], at ED 1, after 10–15 EDs, after 50 EDs, and at subsequent six-month interval visits until 100 EDs were reached, and at the final visit). Blood samples collected at each visit into vacuum-sealed tubes. After centrifugation, they were split in two; one sample was sent to the

local laboratory and the other was transferred to a transport tube, frozen, and sent to the central laboratory (Covance, Inc; Chantilly, VA, USA). If a local laboratory reported an FVIII inhibitor sample as positive, the second sample was analysed by the central laboratory. If this result was also positive, the central laboratory then analysed all available samples for the patient, including the sample from the screening visit. The testing method for FVIII inhibitors was a partial Nijmegen modification of the Bethesda assay procedure using a Beckman Coulter ACL-Elite Coagulation System (Beckman Coulter Inc; Brea, CA, USA). A result of ≥0.6 BU/ml was deemed to be positive. Stability for positive inhibitor control (George King Bio-Medical, Inc; Overland Park, KS, USA), 150 BU/ml diluted 1:75, had been shown for three freeze/thaw cycles, 4 hours (h) at room temperature, and 24 h at 2° to 8°C. Stability of antibodies to insulin stored at ≤20°C has been demonstrated for a duration of at least two years (28), and similar long-term stability was assumed for FVIII inhibitors.

Samples were also collected for anti-FVIII antibody (ADA) analysis using an enzyme-linked immunosorbent assay (ELISA), which was performed at the central laboratory. The ADA was considered positive if the antibody index (increase in ratio of photometric absorbance observed at 405 nm in the patient and normal serum) was greater than 2.34 and when the relative increase in the antibody index was two times that observed at baseline.

Assessments

The primary end point was the proportion of patients with clinically significant FVIII inhibitor development. This was prospectively defined as a central laboratory-confirmed positive inhibitor present in two consecutive samples within a six-week interval along with the need for the patient to administer an alternative haemostatic product to achieve sufficient efficacy or ≥2 reported AEs of decreased drug effect (or another AE indicating a decrease in the efficacy of the test article) within four weeks before the initial or four weeks after the second positive FVIII inhibitor sample collection.

Secondary efficacy end points included the following: annualised bleeding rate (ABR), calculated as the (number of bleeding events/days on treatment regimen) × 365.25 days year; response to the first on-demand treatment with moroctocog alfa (AF-CC) for all new bleeding episodes; number of moroctocog alfa (AF-CC) infusions to treat each new episode; number of breakthrough events within 48 h of a preventive or prophylaxis dose of moroctocog alfa (AF-CC); mean infusion dose and total factor consumption; and the incidence of less-than-expected therapeutic effect (LETE). Response to the first on-demand treatment with study drug was assessed by the patient or a parent/legal representative using a four-point response scale, wherein "excellent" indicated definite pain relief or improvement in bleeding within 8 h of an infusion; "good" indicated definite pain relief or improvement in bleeding within 8 h, with at least one additional infusion administered for complete resolution of the episode or definite pain relief or improvement in bleeding starting 8 h after administration of an infusion; "moderate" indicated probable or slight improvement

starting after 8 h, with at least one additional infusion administered for complete resolution of the episode; and "no response" indicated no improvement at all between infusions or during the 24-h interval following an infusion, or any worsening of the condition. In the on-demand setting, LETE was defined as having two successive "no response" ratings after two successive infusions of moroctocog alfa (AF-CC) administered within 24 h of each other for treatment of the same bleeding event in the absence of confounding factors. In the prophylaxis setting, LETE was defined as a spontaneous bleeding event within 48 h after a regularly scheduled prophylactic dose of moroctocog alfa (AF-CC) in the absence of confounding factors.

Secondary safety end points included the incidence of treatment-emergent AEs (TEAEs), serious AEs (SAEs), and AEs of special circumstance (i.e. inhibitor development).

Blood samples to measure FVIII:C were collected before and 30 minutes (min) after administration of the current FVIII replacement product at screening, as well as before and 30 min after administration of moroctocog alfa (AF-CC) at the study visit. A washout period of at least 72 h from the patient's prior FVIII replacement product or moroctocog alfa (AF-CC) was recommended prior to obtaining the samples. FVIII recovery following the switch to moroctocog alfa (AF-CC) was determined at ED 1 (time of initial exposure to moroctocog alfa [AF-CC]), ED 10–15, ED 50, and ED 100, as well as at 6-month intervals until ED 100 was reached. Plasma samples were analysed for FVIII:C using a validated chromogenic substrate assay (Chromogenix Coamatic Factor VIII Kit; DiaPharma Group, West Chester, OH, USA) at a central laboratory (Covance Laboratories). The lower limit of quantification of the assay was 1 IU/dl (1%). Incremental recovery was calculated as the ratio of change in FVIII:C observed/dose administered and is reported as [IU/dl]/[IU/kg], using the following formula:

$$(\text{FVIII:C}_{0.5h} - \text{FVIII:C}_{pre})/(\text{total dose administered/weight}).$$

Statistical analyses

The sample size estimates for this study were not based on hypothesis testing. Based on a previous study's observed inhibitor rate of 2.2% (27), we estimated for the current study that the enrollment of 150 patients would provide at least a 96% probability to observe inhibitors in one or more patients in one cohort and, for both cohorts combined, 300 patients would provide 99.9% probability. If the true inhibitor rate is instead assumed to be 1.5%, then the probability to observe inhibitors in one or more patients with 150 (planned per cohort) or 300 patients (all planned) would be 90% and 99%, respectively.

All enrolled patients who received at least one dose of moroctocog alfa (AF-CC) were included in the safety and efficacy analyses. All statistical analyses were descriptive, since all patients received the same drug and, as there were no prespecified hypotheses, no tests of hypotheses were performed. Data for incremental recovery were also analysed using descriptive statistics.

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Data for a subgroup of paediatric patients (aged 12–17 years) were also examined separately, but no formal comparisons were made between the overall and paediatric populations.

Results

Patients

This study was conducted from May 2009 to March 2013 and was terminated early by agreement with the EMA before full recruitment was attained. The study enrolled a total of 208 patients. If the true inhibitor rate was 2.2% or 1.5%, then the probability to observe inhibitors in 1 or more of the 208 patients would be 99% and 96%, respectively.

All 208 enrolled patients were male, and all received at least one dose of moroctocog alfa (AF-CC) (cohort 1, n = 146; cohort 2, n = 62). A total of 177 (85.1%) patients completed the study and 31 (14.9%) patients discontinued. A similar percentage of patients completed the study in each cohort (84.2% and 87.1%, in cohorts 1 and 2, respectively). The most common reasons for discontinuation were miscounted EDs (n = 7), patient request (n = 5), and protocol violation (n = 5). No patient discontinued because of lack of efficacy, and a single patient in cohort 1 discontinued because of an AE.

Of the 208 patients enrolled, 42 were paediatric patients (cohort 1, n = 33; cohort 2, n = 9). A total of 35 (83.3%) paediatric patients completed the study and 7 (16.7%) discontinued. The most common reason for discontinuation was "other" (n=4); no discontinuations were attributed to lack of efficacy or an AE.

There were no notable differences in baseline characteristics between the two cohorts (▶Table 1). The mean age of patients was 30.5 years and most patients were white. Overall, 118/205 patients (57.6%) had a family history of haemophilia, 142/208 (68.3%) had target joint involvement, and 18/206 (8.7%) had a personal history of inhibitors to FVIII products. At baseline, 58 (27.9%) patients were receiving treatment as a primary prophylaxis regimen, 96 (46.2%) were on a secondary prophylaxis regimen, two (1.0%) were on preventive therapy, and 52 (25.0%) were on an on-demand regimen. The mean number of EDs on study was 94 (range, 1–139; 95% confidence interval [CI]: 91–97).

At baseline, the mean age in the paediatric subpopulation was 14.8 (range, 12–17) years, and 97.6% were white. The mean duration of therapy was 324 (± 171) days, and was longer in cohort 2 (499 days) compared with cohort 1 (277 days).

Primary end point

No clinically significant FVIII inhibitors were reported during the study. For the given sample size of 208 patients with 0 inhibitors observed, the true inhibitor rate of 1.5% or higher can be excluded with 95.7% probability. Four patients (2 adults and 2 paediatric patients), all in cohort 1, had positive inhibitor results as measured locally on six occasions: at month 6 visit (1 BU) and at an unplanned visit about one month later (>0.6 BU) in the first patient; at month 12 in the second (positive BU [exact value not

reported]); at visits for ED 1 (0.7 BU) and 10–15 (0.7 BU) in the third; and at visit for ED 100 (0.7 BU) in the fourth. However, none of these inhibitors were confirmed by the central laboratory, and no inhibitor-related clinical manifestations were reported. Corresponding anti-FVIII antibody results were also negative. For all four patients, administration of alternative haemostatic products was not required and no instance resulted in discontinuation from the study. As patients did not have any clinical manifestations, there were no changes in dose or regimen. Per the protocol, all four local laboratory-determined positive anti-FVIII antibody results were reported as AEs of special circumstance and were considered SAEs.

Secondary end points

The median ABR was 23.4 in patients categorised at baseline as following an on–demand treatment regimen (52 patients with bleeding events), 1.1 in patients following a preventive regimen (2 patients with bleeding events), and 3.4 in patients following a prophylaxis regimen (154 patients with bleeding events). In the paediatric subpopulation, the median ABR was 40.9 in patients following an on-demand treatment regimen (8 patients with bleeding events) and 3.0 in patients following a prophylactic regimen (34 patients with bleeding events). None of the paediatric patients was categorised at baseline as following a preventive regimen.

Overall, 156 patients reported 3,241 bleeding episodes. The number of infusions required to treat each new bleeding episode, by response to the first infusion, are summarised in ▶Table 2. In total, 26 of 3,241 (0.8%) total first infusions were rated as having

Table 1: Demographic and baseline characteristics.

Characteristic	Cohort 1[a] (n=146)	Cohort 2[b] (n=62)	Total (N=208)
Age, years			
Mean (SD)	30.1 (13.2)	31.6 (12.5)	30.5 (13.0)
Median (min–max)	29.0 (12.0–64.0)	30.0 (12.0–58.0)	29.0 (12.0–64.0)
Age category, n (%)			
12–17	33 (22.6)	9 (14.5)	42 (20.2)
18–65	113 (77.4)	53 (85.5)	166 (79.8)
Race, n (%)			
White	139 (95.2)	62 (100.0)	201 (96.6)
Asian	2 (1.4)	0	2 (1.0)
Black	1 (0.7)	0	1 (0.5)
Other	4 (2.7)	0	4 (1.9)
Therapy duration, days, n[c]			
Mean (SD)	357 (225)	376 (222)	363 (224)

[a]Switched from moroctocog alfa. [b]Switched from other FVIII replacement product. [c]Number of days from first dose to last dose. Max, maximum; min, minimum; SD, standard deviation.

Response to first infusion	Bleeding events, n (%)	Number of infusions for resolution	
		Mean (SD)	Median (min–max)
Excellent	1650 (50.9)	1.1 (0.7)	1 (1–18)
Good	1031 (31.8)	1.4 (1.5)	1 (1–31)
Moderate	191 (5.9)	2.0 (1.6)	2 (1–12)
No response	26 (0.8)	2.5 (2.6)	1 (1–11)
Data not recorded	343 (10.6)	1.3 (1.6)	1 (1–20)
Total (any)	3241	1.3 (1.2)	1 (1–31)
SD, standard deviation.			

Table 2: Summary of responses to first infusion of moroctocog alfa (AF-CC) administered to treat a bleeding episode.

"no response." The majority of bleeding episodes (2,804/3,241 [86.5%]) resolved after one infusion of moroctocog alfa (AF-CC), and the responses to the majority of first infusions (82.7%) were rated as "excellent" or "good." In the paediatric subpopulation, 34 patients reported 645 bleeding episodes. Excellent and good responses accounted for 87.6% of responses to a first infusion.

The overall incidence of LETE was 0.06% (2 reports of LETE in 3,241 bleeding episodes; 95% CI: 0.01–0.22) in the on-demand setting and 0.19% (21 reports of LETE in 11,262 prophylactic infusions; 95% CI, 0.12–0.28) in the prophylaxis setting. In paediatric patients, the LETE rate in the on-demand setting was 0.16% (1 report of LETE in 645 bleeding episodes; 95% CI, 0.00–0.86) and 0.24% in the prophylaxis setting (5 reports of LETE in 2,050 prophylactic infusions; 95% CI, 0.08–0.57).

Overall, 33 patients experienced 96 breakthrough bleeding events within 48 h after a prophylactic infusion of moroctocog alfa (AF-CC) but etiology was not collected in the patient diary. A total of 108 patients received at least one prophylactic infusion then experienced a bleeding event. The majority of bleeding episodes (527/833 [63.3%]) occurred >72 h after the prophylactic dose.

In patients categorised at baseline as following a nonprophylactic regimen, the median dose per patient was 28.5 IU/kg/infusion, and the median annualised total factor consumption was 1,825 IU/kg/infusion per patient. Correspondingly, in the eight paediatric patients, the median dose per patient was 27 IU/kg/infusion and

Table 3: Treatment-emergent adverse events occurring in >5% of patients.

Event, n (%)	Patients (N=208)*	Events
Any AE	147 (70.7)	731
Nasopharyngitis	32 (15.4)	44
Arthralgia	26 (12.5)	69
Haemarthrosis	24 (11.5)	86
Headache	22 (10.6)	48
Limb injury	15 (7.2)	25
Influenza	13 (6.3)	18
*Number of patients who reported ≥1 treatment emergent AE. AE, adverse event.		

the median annualised total factor consumption was 1,466 IU/kg per patient. For patients categorised at baseline as following a prophylaxis regimen, median dose per infusion was 30 IU/kg and median annualised total factor consumption was 4,085 IU/kg per patient. For the 34 paediatric patients following a prophylaxis regimen, the median dose per patient was 30 IU/kg/infusion, and the median annualised total factor consumption was 4,795 IU/kg per patient.

Safety

Overall, 147 (70.7%) patients reported at least one TEAE. The most frequently reported TEAEs were nasopharyngitis and arthralgia (►Table 3). The majority of TEAEs were reported as mild or moderate, and none were considered life-threatening. Thirteen TEAEs considered severe occurred in 10 patients: FVIII inhibitors (as a result of local testing) were reported as severe in two patients, and urinary tract infection, epistaxis, haemarthrosis, haematoma, septic arthritis streptococcal, acute abdomen, intestinal haematoma, spontaneous haematoma, bronchitis, intestinal obstruction, and tooth fracture were each reported as severe in one patient, with some patients experiencing more than one event. Other than FVIII inhibition, which was considered to be related to moroctocog alfa (AF-CC) treatment, the other severe AEs were considered unrelated. One patient discontinued because of acute abdomen and intestinal haematoma.

A total of 31 SAEs were reported by 20 patients (9.6%). The most common SAE was factor VIII inhibition, reported in five patients (2.4%) following testing at local laboratories. None of the cases of FVIII inhibition were confirmed as positive by the central laboratory and thus did not meet the criteria for clinical significance, as previously described. All events of FVIII inhibition resolved without leading to treatment discontinuation. All other SAEs occurred in one patient each and were single instances, except for two episodes of musculoskeletal stiffness in a single patient.

Pharmacokinetic assessments

Incremental recovery in the two cohorts over the study period is shown in ►Figure 1. The recovery remained relatively constant after 100 EDs and up to 24 months of use, although fewer

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Figure 1: Mean ± SD incremental recovery of FVIII:C over time in previously treated patients with haemophilia A. *Other indicates other factor VIII replacement products.
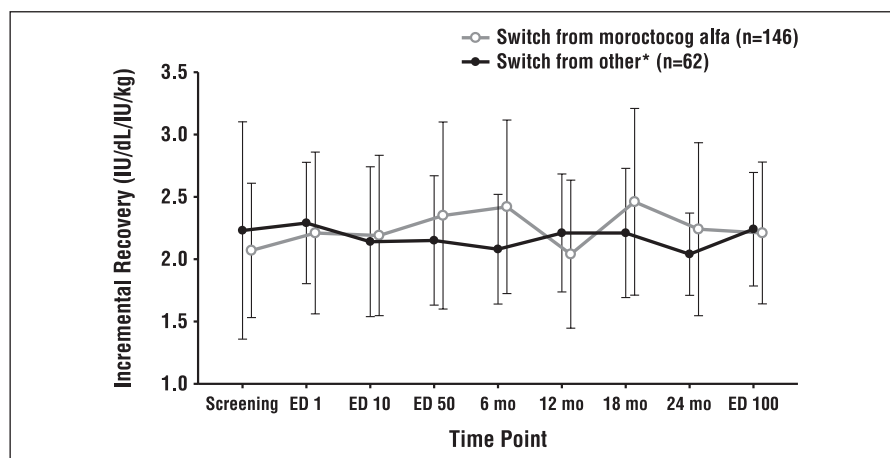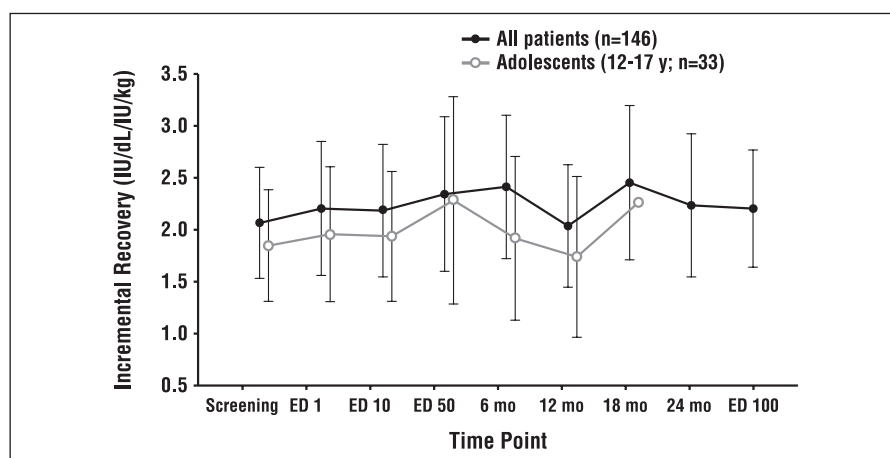

Figure 2: Mean ± SD incremental recovery in previously treated patients with haemophilia A. ED, exposure day.

observations were made at later time periods. Mean recovery at the screening visit was 2.12 (± 0.66) IU/dl/IU/kg, and ranged between 2.09 and 2.36 IU/dl/IU/kg over the duration of the study. There appeared to be no difference in the recovery observed at baseline between patients taking moroctocog alfa (2.07 ±0.54 IU/dl/IU/kg; n = 146) and those taking other replacement products (2.23 ±0.87 IU/dl/IU/kg; n = 62), with similar values observed between both cohorts throughout the study. The mean recovery observed in the paediatric subpopulation was generally lower than the mean recovery observed for the overall population, as shown in ►Figure 2. At month 6, mean recovery in the paediatric group was 1.92 (±0.80) IU/dl/IU/kg vs 2.35 (±0.66) IU/dl/IU/kg in the overall population.

Discussion

This prospective postauthorisation safety surveillance study monitored the development of clinically significant and laboratory-confirmed inhibitors in a population of previously treated male patients, 12 years of age or older, with severe haemophilia A transitioning from moroctocog alfa or other FVIII replacement products to moroctocog alfa (AF-CC). No clinically significant FVIII

inhibitor development was noted after patients switched to moroctocog alfa (AF-CC). None of the five locally reported positive FVIII inhibitor results were confirmed centrally, no inhibitor-related clinical manifestations were reported, and corresponding anti-FVIII antibody assays were negative.

This study demonstrated that moroctocog alfa (AF-CC) was effective in controlling or preventing bleeding episodes in patients switching from moroctocog alfa or other FVIII product. A majority of bleeding episodes (86.5%) were managed with a single infusion of moroctocog alfa (AF-CC), with excellent or good responses to the first infusion. In patients receiving primary or secondary prophylaxis, only 30% experienced breakthrough bleeding events. Inhibitor development and efficacy findings in paediatric patients (aged 12–18 years) were similar to those observed in the overall population.

Pharmacokinetic analysis showed that although there was variability between patients, recovery remained consistent over 100 EDs or 24 months of treatment after switching to moroctocog alfa (AF-CC), further substantiating its efficacy. Previous studies also demonstrated stable pharmacokinetics of moroctocog alfa over periods of up to 12 months (27, 29). When the subgroup of paediatric patients was analysed separately, recovery was modestly lower throughout the study. Lower recovery after FVIII

replacement therapy in children has been reported by others, thought to be due to differences in body composition compared with adults (30–32). Younger, leaner patients may have larger blood volumes than older, heavier patients when normalised by weight (33). Thus, when the same weight-based doses of FVIII replacement products are administered, a lower peak FVIII:C and, consequently, a lower recovery may be observed.

Ongoing debate has centred on the relationship between FVIII replacement product and inhibitor risk (34, 35). A switch to a different product may be a preferable option for many patients because of improved safety, fewer side effects (allergic reactions), convenience of administration, price, national contracting, and patient preference (23). However, clinicians have often been reluctant to switch FVIII replacement products that patients are using because of a perceived increased risk of inhibitor development. A recently conducted DELPHI analysis regarding product switching and inhibitor development concluded that current practices regarding switching treatments in haemophilia is influenced not by clinical evidence but by a fear of developing inhibitors (24). This concern stemmed from two inhibitor outbreaks in patients switching from their usual plasma-derived product to new products subjected to modified viral inactivation methods (36, 37), which likely

What is known about this topic?

- Historically, prescribers have been reluctant to switch between FVIII products because of a perceived increased risk of inhibitor formation with a new product.
- Several large prospective and retrospective studies have reported a low risk of inhibitor development following a switch in FVIII replacement products.
- Moroctocog alfa (AF-CC), a third-generation B-domain–deleted recombinant factor VIII product for hemophilia A, was developed as a successor to moroctocog alfa; in clinical studies, the risk of inhibitors with moroctocog alfa (AF-CC) was similar to that observed with moroctocog alfa and other recombinant FVIII products.

What does this paper add?

- This prospective, postauthorisation safety surveillance study conducted in previously treated patients with severe haemophilia A found that transitioning from moroctocog alfa or other FVIII replacement products to moroctocog alfa (AF-CC) did not increase the risk of inhibitor formation following the switch.
- Moroctocog alfa (AF-CC) was effective in the treatment of haemophilia A after switching from moroctocog alfa or other FVIII replacement products, as assessed by ABR, incidence of LETE, number of infusions required to treat a bleeding event, and incidence of breakthrough bleeding events.
- Patients had stable recovery after switching for two years.
- The data support the safety of switching from previous recombinant or plasma-derived FVIII products to moroctocog alfa (AF-CC).

resulted in the generation of neoantigens. A recent meta-analysis of prospective clinical studies in previously treated patients showed a seven-fold increased risk of *de novo* inhibitors with B-domain deleted rFVIII compared with the full-length molecule, suggesting that recombinant products may differ in immunogenicity (38). This analysis has been criticised, however, because of the small number of *de novo* inhibitors, the heterogeneity of the studies analysed, and the lack of a comparator group.

In contrast, several large prospective and retrospective studies have reported a low risk of inhibitor development following a switch in patients' FVIII replacement products (12–14, 39–42), corroborating the results of our current study. Specifically, findings for three national product switches have been reported to date, and all reported low rates of inhibitor development after the switch. In Ireland, 113 patients with haemophilia A were required to switch to Advate (Baxter Healthcare Corporation) (41) and, in Canada, 274 patients were required to switch to Kogenate (Bayer HealthCare Pharmaceuticals, Inc) (40). The development of *de novo* inhibitors after switching was low in both registries (0.9 % for the Irish registry; 0 % for the Canadian registry). More recently, national contracting requirements in the UK required half of the patients receiving rFVIII products to switch brands to moroctocog alfa (AF-CC), allowing for the first investigation to date of inhibitor incidence in both switchers (n=535) and non-switchers (n=682) (42). The rate of inhibitors was low for both the switchers (0.75 %) and the non-switchers (0.1 %), and no significant differences were observed between the two groups. Further, in two global clinical studies of moroctocog alfa (AF-CC) in previously treated patients, Recht et al. (27) reported that only three of 204 patients developed low-titre inhibitors *de novo*. These studies, in addition to the findings from the current study, indicate that the risk of *de novo* inhibitor development is not increased in patients switching among FVIII replacement products.

Regulatory authorities require immunogenicity assessment of new FVIII products in previously treated patients (43–45); however, the low inhibitor rate in these makes comparison among different products difficult. As described by Iorio et al., a number of study designs (e.g. nested case-control, randomised control, cohort, case series, postmarketing surveillance) may be used to assess the immunogenicity related to switching, with the risk of bias and whether baseline risk is accounted for varying based on the study perspective (retrospective or prospective) and the rigor of observation (controlled or uncontrolled). Randomised controlled trials reduce the risk of bias and control for baseline risk, and represent the highest-level study design (23). However, these trials are often limited in their power to detect adverse events, particularly those that are uncommon, such as inhibitor formation in previously treated patients (46). Postmarketing surveillance studies provide an alternative means to determining whether FVIII replacement products may pose an increased risk of inhibitor development. This study collected information prospectively over an extended period of time from a heterogeneous, "real-life" patient population. The use of both local and central laboratories for monitoring the development of inhibitors allowed for consistent and standardised data collection and assessment, and laboratory

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assessments for FVIII inhibitors were conducted at numerous time points to ensure complete detection of all inhibitors. The discrepancy between local and central laboratory findings observed in this study is not surprising given the inter-laboratory variation that has been reported in the literature for the Nijmegen modified assay (≈30 %) (47), further validating the importance of using both local and central laboratories for the assessment of inhibitors. Additionally, care was taken to collect samples for inhibitor testing after an appropriate washout of replacement therapy, to prevent interference with the inhibitor assay, and anti-FVIII antibody testing was performed.

In summary, no clinically significant FVIII inhibitor development, new safety risks or concerns, or complications associated with efficacy or safety, were noted in this postauthorisation safety surveillance study in previously treated patients with severe haemophilia A transitioning from moroctocog alfa or other FVIII replacement products to moroctocog alfa (AF-CC). Findings from this study confirm the lack of neo-antigenicity of moroctocog alfa (AF-CC) and support the safety of switching to moroctocog alfa (AF-CC) from other FVIII replacement products.

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