# Postauthorization Safety Surveillance Study (PASS) of Hemophilia 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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## ABSTRACT

**Objectives:** To fulfill a European Medicines Agency requirement, this PASS assessed clinically significant inhibitor development in patients (pts) with severe hemophilia A transitioning from moroctocog alfa or other factor VIII (FVIII) replacement products to reformulated moroctocog alfa (AF-CC).

**Methods:** This nonrandomized, prospective, interventional, open-label study enrolled males ≥12y with severe hemophilia A (FVIII:C <0.01 IU/mL), >150 exposure days to recombinant or plasma-derived FVIII products, and no detectable inhibitor at screening. Pts were assigned to cohorts based on if they were transitioning to moroctocog alfa (AF-CC) from moroctocog alfa (cohort 1) or from another recombinant or plasma-derived FVIII product (cohort 2). Primary safety end point was proportion of pts with clinically significant FVIII inhibitor development. Secondary efficacy and safety end points included annualized bleeding rate (ABR), less-than-expected therapeutic effect (LETE), and adverse events (AEs).

**Results:** 208 pts were enrolled (cohort 1, n=146; cohort 2, n=62). Mean age was 30.5y (range 12–64), with 80% of pts aged >18y. Mean number of exposure days was 94 (range 1–139). No clinically significant FVIII inhibitors were reported. Although 6 local positive FVIII inhibitors were reported in 4 pts, none were confirmed centrally, no inhibitor-related clinical manifestations were reported, and anti-FVIII antibody assays were negative. Median ABRs were 23.4 and 3.4 following on demand (n=52) and prophylaxis (n=154) regimens at baseline, respectively. LETE was 0.06% during on-demand treatment and 0.19% in the prophylaxis setting. Overall, 147 (71%) pts reported ≥1 treatment-emergent AE, most commonly (>5%) nasopharyngitis (15%), arthralgia (13%), hemarthrosis (12%), headache (11%), limb injury (7%), and influenza (6%); 20 (9.6%) patients reported ≥1 serious AE, most commonly (>1%) FVIII inhibition (2%).

**Conclusions:** Historically, there has been reluctance to change the type of factor replacement product that pts with hemophilia are using because of a perceived increase in risk of inhibitor development. During this PASS in previously treated males aged ≥12y with severe hemophilia A transitioning from moroctocog alfa or other FVIII replacement products to moroctocog alfa (AF-CC), no clinically significant FVIII inhibitor development was noted. Efficacy and safety results were similar to previous studies.

## INTRODUCTION

- Patients with hemophilia A are at risk of developing neutralizing antibodies, also referred to as inhibitors, in response to replacement therapy with factor VIII (FVIII)[1]
- Clinically significant inhibitors are one of the most serious and costly complications of hemophilia treatment, requiring the use of large doses of replacement factors or bypassing agents[2]
  - Approximately 20% to 30% of previously untreated patients with severe hemophilia A develop inhibitors[3]
- 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 patients with hemophilia A[4]
  - It is produced using a modification of the previous process used to manufacture moroctocog alfa (ReFacto®; Wyeth Pharmaceuticals, Inc. [Pfizer], Philadelphia, PA, USA) that eliminates 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[5]
  - Two clinical studies confirmed that the risk of developing inhibitors to FVIII after administration of moroctocog alfa (AF-CC) is comparable to that observed with its predecessor, moroctocog alfa[6]
- Clinicians are often reluctant to switch between FVIII products because of a concern it may trigger the development of inhibitors; however, switching may be a reasonable approach for various reasons (safety, economical, preference, etc)[7]
  - To date, available data from prospective and retrospective studies have not found an increased risk of inhibitor development after FVIII product switch[8-10]
- This study was conducted to fulfill a European Medicines Agency (EMA) requirement for postauthorization safety surveillance and risk management and to ensure that moroctocog alfa (AF-CC) had an acceptable rate of inhibitor development

## OBJECTIVE

- This postauthorization safety surveillance study was conducted to assess clinically significant inhibitor development in patients with severe hemophilia A transitioning from moroctocog alfa or other FVIII replacement products to reformulated moroctocog alfa (AF-CC) in usual care settings

## METHODS

### Patients

- Male patients aged ≥12 years with severe hemophilia A (FVIII:C <1%) with a treatment history of >150 exposure days (EDs) to prior recombinant or plasma-derived FVIII replacement products were eligible for study enrollment
- Key exclusion criteria
  - Presence of any bleeding disorder in addition to hemophilia A
  - For laboratory assessment, any measured Bethesda inhibitor titer ≥0.6 BU, regardless of the laboratory normal range, or any Bethesda inhibitor titer >upper limit of normal for the testing laboratory at the time of screening
  - Treated with immunomodulatory therapy (including immune tolerance induction) during the screening period
  - Known hypersensitivity to hamster protein
  - Prior exposure to moroctocog alfa (AF-CC)

### Study Design

- This was a prospective, interventional, open-label study
- Following screening, all enrolled patients were assigned to 1 of 2 cohorts as follows:
  - Cohort 1: patients transitioning from moroctocog alfa to moroctocog alfa (AF-CC)
  - Cohort 2: patients transitioning from another recombinant or plasma-derived FVIII product to moroctocog alfa (AF-CC)
- All patients received moroctocog alfa (AF-CC) at a dose and frequency prescribed by their treating physician per local standard of care and in accordance with the Summary of Product Characteristics
- Patients maintained a paper infusion log that could be used to track EDs, reason for infusion (eg, on demand, preventive, or prophylaxis), and assessments of on-demand infusions given to treat bleeding episodes
- Study visits were based on ED milestones (ED 1, 10–15 EDs, and 50 EDs), as well as time-based visits at 6-month intervals (not required if scheduled ±60 days of ED milestone visits)
- The final visit was to occur after 100 EDs were achieved. A follow-up phone call was to be conducted at least 28 days after the final visit to collect information on adverse events (AEs)
- Laboratory assessments for FVIII inhibitors were conducted during the study at screening (on prior FVIII therapy, before switching to moroctocog alfa [AF-CC]), at ED 1, after 10–15 EDs, at 50 EDs, at subsequent 6-month interval visits, and at final visit)
  - At each visit, collected samples were split in two; one sample was sent to the local laboratory and the other was sent to the central laboratory. If a local laboratory reported an FVIII inhibitor sample as positive, the second sample was analyzed by the central laboratory. If an FVIII inhibitor sample was considered positive by the central laboratory, the central laboratory then analyzed all available samples for the patient, including the sample provided from the screening visit
  - Anti-FVIII antibody analyses (enzyme-linked immunosorbent assay [ELISA]) were conducted by the central laboratory if the inhibitor assay conducted by the local laboratory was positive. A positive ELISA response was defined as an antibody index >2.34 and a relative increase in the antibody index 2 times that observed at baseline

### Assessments

- The primary safety end point was the proportion of patients with clinically significant FVIII inhibitor development, defined as a central laboratory-confirmed positive inhibitor (≥0.6 BU using a partial Nijmegen modification of the Bethesda assay present at 2 consecutive blood draws within a 6-week interval) and 1 of the following within 4 weeks before the initial or within 4 weeks following the second positive FVIII inhibitor sample collection:
  - The need for the patient to administer alternative hemostatic products to achieve sufficient efficacy
  - ≥2 reported AEs of decreased drug effect
- Secondary efficacy and safety end points included:
  - Annualized bleeding rate (ABR)
  - Responses to first on-demand treatment with moroctocog alfa (AF-CC) for all new bleeding events, as assessed by the patient on a 4-point scale (excellent, good, moderate, or no response)
  - Incidence of less-than-expected therapeutic effect (LETE)
    - On-demand setting: 2 successive "no response" ratings after 2 successive infusions of moroctocog alfa (AF-CC) administered within 24 hours of each other for treatment of the same bleeding event in the absence of confounding factors
    - Prophylaxis setting: spontaneous bleeding event within 48 hours after a regularly scheduled prophylactic dose of moroctocog alfa (AF-CC) in the absence of confounding factors
  - Number of infusions to treat each new bleeding event
  - Number of breakthrough bleeding events within 48 hours of a preventative/prophylactic dose of moroctocog alfa (AF-CC)
  - Mean infusion dose and total factor consumption
  - Incidence of treatment-emergent AEs (TEAEs) and serious AEs (SAEs)

### Statistical Analyses

- The study planned to enroll approximately 300 patients at approximately 120 sites
- All statistical analyses were descriptive, since all subjects received the same drug, and, as there were no prespecified hypotheses, no tests of hypotheses were performed
- All enrolled patients who took ≥1 dose of moroctocog alfa (AF-CC) were included in the safety and efficacy analyses

## RESULTS

### Patient Disposition

- The study was terminated early by agreement with the EMA before full recruitment was attained; however, this was not considered to affect the overall results
- In total, 208 male patients were enrolled in the study and received at least 1 dose of moroctocog alfa (AF-CC) (cohort 1, n=146; cohort 2, n=62)
  - 177 (85.1%) patients completed the study, and 31 (14.9%) patients discontinued
    - The most common reasons for discontinuation were miscounted EDs (n=7), patient request (n=5), and protocol violation (n=5); no patients discontinued the study due to lack of efficacy and a single patient in cohort 1 discontinued because of an AE
  - The mean (min–max) number of EDs was 94 (1–139)
- Demographics and baseline characteristics were generally similar between the two cohorts
  - The majority of patients were white (97%) and the mean (min–max) age was 30.5 (12–64) years, with 79.8% of patients aged >18 years (**Table 1**)
- At baseline, 58 (27.9%) patients continued with a primary prophylaxis regimen, 96 (46.2%) were on a secondary prophylaxis regimen, 2 (1.0%) were on preventive therapy, and 52 (25.0%) were on an on-demand regimen

**Table 1. Summary of Demographics and Baseline Characteristics**

| Characteristic | Cohort 1 (n=146) | Cohort 2 (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) | 201 (96.6) |
| Asian | 2 (1.4) | 0 | 2 (1.0) |
| Black or African American | 1 (0.7) | 0 | 1 (0.5) |
| Other | 4 (2.7) | 0 | 4 (1.9) |
| Therapy duration* | | | |
| Mean (SD) | 357 (225) | 376 (222) | 363 (224) |

*Number of days from first dose to last dose.
Max, maximum; min, minimum; SD, standard deviation.

### Primary End Point

- No clinically significant FVIII inhibitors were reported during the study
  - Although 6 local positive FVIII inhibitors were reported in 4 patients (all in Cohort 1), none were confirmed centrally, no inhibitor-related clinical manifestations were reported, and corresponding results of anti-FVIII antibody assays (ELISA) were negative
  - For all 4 patients, administration of alternate hemostatic products was not required and no instance resulted in discontinuation from the study
  - Per protocol, all 4 laboratory-determined positive anti-FVIII antibody results were reported as AEs of special circumstance and were considered SAEs

### Secondary End Points

- Overall, 156 patients reported 3241 bleeding episodes
- The median ABR was 23.4 in patients following baseline on-demand treatment (n=52), 1.1 in those following baseline preventive treatment (n=2), and 3.4 in those following baseline prophylaxis treatment (n=154)
  - The number of infusions required to treat each new bleeding episode, by response to first infusion, are summarized in **Table 2**
  - The majority (82.7%) of first infusions of moroctocog alfa (AF-CC) were rated "excellent" or "good"
  - Most (2804/3241, 86.5%) bleeding episodes resolved after 1 infusion of moroctocog alfa (AF-CC)

**Table 2. Summary of Response to First Infusion of Moroctocog Alfa (AF-CC) and Number of Infusions Administered to Treat a Bleeding Episode**

| 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) |

- The overall incidence rate of LETE was 0.06% (2 LETE bleeding events from 3241 bleeding episodes) during on-demand treatment and 0.2% (21 LETE bleeding events from 11262 prophylaxis infusions) in the prophylaxis setting
- In total, 33 patients experienced 96 breakthrough bleeding events within 48 hours after a prophylactic infusion of moroctocog alfa (AF-CC)
  - Mean (SD) number of bleeding events was 2.9 (2.0)
- For patients following a non-prophylaxis regimen at baseline, the median dose per moroctocog alfa (AF-CC) infusion was 28.5 IU/kg and the median annualized total factor consumption was 1825 IU/kg per patient. For patients following a prophylaxis regimen at baseline, median dose per infusion was 30 IU/kg and median annualized total factor consumption was 4085 IU/kg per patient

### Safety

- Overall, 147 (70.7%) patients reported ≥1 TEAE; the most common are summarized in **Table 3**
  - The majority of TEAEs were assessed as mild or moderate in severity; no life-threatening TEAEs were reported

**Table 3. Treatment-Emergent Adverse Events Occurring in >5% of Patients**

| Event | Patients, n (%) (N=208)* | Events, n |
|---|---|---|
| Any AE | 147 (70.7) | 731 |
| Nasopharyngitis | 32 (15.4) | 44 |
| Arthralgia | 26 (12.5) | 69 |
| Hemarthrosis | 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.

- Overall, a total of 20 (9.6%) patients reported 31 SAEs
  - The most common (>1%) SAE was FVIII inhibition (n=5; 2.4%)
  - Four of the cases of FVIII inhibition (from local laboratory analyses) were not confirmed as positive by the central laboratory, as previously described; in the other case, there was no "positive" laboratory result and the event was reported in error
- Only 1 patient discontinued from the study because of AEs of acute abdomen and intestinal hematoma

## CONCLUSIONS

- No clinically significant FVIII inhibitor development was noted during this prospective postauthorization safety surveillance study in previously treated males aged ≥12 years with severe hemophilia A transitioning from moroctocog alfa or other FVIII replacement products to moroctocog alfa (AF-CC)
- Moroctocog alfa (AF-CC) was efficacious in the treatment of hemophilia 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
- No new safety risks or concerns were observed for previously treated patients administered moroctocog alfa (AF-CC) after switching from moroctocog alfa or other FVIII products in the usual care setting
- Overall, in this study of patients with severe hemophilia A, no complications associated with the efficacy or safety of moroctocog alfa (AF-CC) were reported after switching from moroctocog alfa or another recombinant or plasma-derived FVIII product

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