PT012

Assessment of Incremental Recovery Over Time in 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: The goal of this portion of the larger clinical study was to assess recovery in all patients up to 24 months or exposure day 100 after switching to moroctocog alfa (AF-CC).

Methods: Patients aged ≥12 years with severe hemophilia A (FVIII:C <1%), >150 exposure days to recombinant or plasma-derived FVIII products, and no detectable inhibitor at screening were enrolled in the study. Blood samples to measure FVIII activity (FVIII:C) were collected before and 30 minutes after administration of 50 IU/kg of their current FVIII replacement product at screening as well as before and after 50 IU/kg doses of moroctocog alfa (AF-CC) administered on exposure days (EDs) 1, 10–15, 50, and 100 as well as at months 6, 12, 18, and 24 after entry into the study. FVIII:C was assayed at a central laboratory using a validated chromogenic assay. Recovery was calculated as the ratio of change in FVIII:C observed/dose administered.

Results: Mean ± SD screening recovery was 2.07 ± 0.54 IU/dL/IU/kg in 146 patients switching from ReFacto and 2.23 ± 0.87 IU/dL/IU/kg in 62 patients switching from other replacement products. Although there was overlap, mean recovery observed in the 42 adolescents aged 12 to 17 years who took part in the trial was lower than mean recovery observed in all patients (screening: 1.94 ± 0.55 IU/dL/IU/kg [adolescents]; 2.12 ± 0.66 IU/dL/IU/kg [all patients]).

Conclusions: Although there was variability between, and among, individuals, recovery remained consistent over 100 EDs or 24 months of treatment after switching to moroctocog alfa (AF-CC). This study's contribution to the current practice/evidence base of hemophilia is the demonstration of consistent recovery over 100 EDs or 24 months of moroctocog alfa (AF-CC) treatment and robust assessment of intersubject variability (CV 24%–30%) after switching the patients from moroctocog alfa, or another FVIII product, to moroctocog alfa AF-CC, over a prolonged period under usual care settings.

INTRODUCTION

- 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[1]
  - 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[2]
- Pharmacokinetic equivalence was shown for recovery between moroctocog alfa and a full-length recombinant factor VIII (FVIII) concentrate in 30 patients (2.35 ± 0.47 and 2.39 ± 0.65 IU/dL/IU/kg, respectively, with a 90% log-transformed confidence interval [CI] of the ratio 92.5%–108%)[3] using a one-stage clotting assay to measure activity
- Recovery was shown to be stable over a period of 6 months of moroctocog alfa therapy in 25 patients[3]
- The assessment of recovery reported here is part of a larger study 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

- To assess recovery over time in all patients participating in 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 >150 exposure days (EDs) to moroctocog alfa (AF-CC) or other recombinant or plasma-derived FVIII products, transitioning to moroctocog alfa (AF-CC), and with no detectable inhibitor at screening were eligible for study enrollment

Study Design

- This was a nonrandomized, 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)
- Recovery was assessed during study visits, which 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

Assessments

- Blood samples to measure FVIII activity (FVIII:C) were collected before and 30 minutes after administration of 50 IU/kg of their current FVIII replacement product at screening as well as before and 30 minutes after 50 IU/kg doses of moroctocog alfa (AF-CC) administered at the study visit
- FVIII:C was assayed at a central laboratory using a validated chromogenic assay
- The lower limit of quantification of the assay was 1 IU/dL (1%)
- Recovery was calculated as the ratio of change in FVIII:C observed/dose administered using the equation below:

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

Statistical Analyses

- Summary statistics were calculated using all recovery values observed at each office visit for all patients and separately for patients aged 12 to 17 years

RESULTS

- The ages and treatment duration for patients participating in the study are shown in **Table 1**
- Incremental recovery is shown in **Table 2** as well as in **Figures 1** and **2**
- Although no statistical comparison was made, there appeared to be no difference in the recovery observed at screening 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)

Table 1. Summary of Age and Treatment Duration

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 years	33 (22.6)	9 (14.5)	42 (20.2)
18–65 years	113 (77.4)	53 (85.5)	166 (79.8)
Therapy duration†			
Mean (SD)	357.3 (224.9)	375.7 (221.7)	362.8 (223.6)

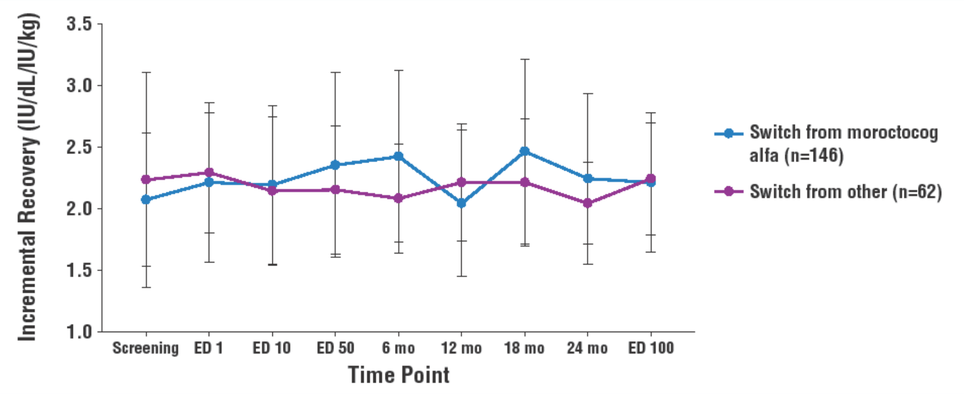
*Cohort 1: switched from moroctocog alfa; Cohort 2: switched from other factor VIII replacement.
†Number of days from first dose to last dose.
Max, maximum; min, minimum; SD, standard deviation.

Table 2. Mean Incremental Recovery in Previously Treated Patients After 50 IU/kg Moroctocog Alfa (AF-CC) (All Patients)

	Time Point						
Parameter	ED 10–15	ED 50	ED 100	Month 6	Month 12	Month 18	Month 24
N	192	182	179	74	33	24	11
Mean	2.18	2.29	2.22	2.35	2.09	2.36	2.16
SD	0.63	0.69	0.54	0.66	0.56	0.67	0.58

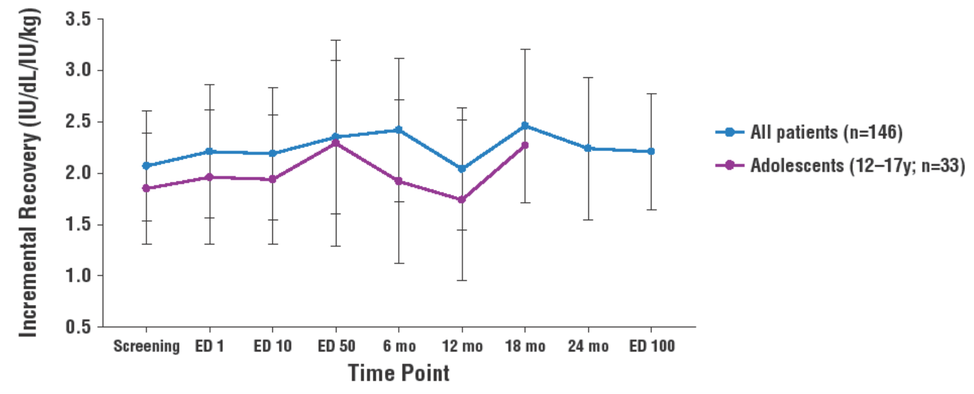
ED, exposure day; SD, standard deviation.

Figure 1. Mean ± SD Incremental Recovery Data (All Patients)



ED, exposure day.

Figure 2. Mean ± SD Incremental Recovery Data (All Patients Switching from Moroctocog Alfa)



ED, exposure day.

CONCLUSIONS

- There was no impact of previous FVIII replacement on incremental recovery observed after administration of moroctocog alfa (AF-CC)
- The mean recovery observed in adolescents aged 12 to 17 years was usually lower than the mean recovery observed for all patients, aged 12 to 64 years
- Incremental recovery values remained unchanged after 100 EDs and up to 24 months of use

REFERENCES

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