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REVIEW ARTICLE

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Clinical experience with moroctocog alfa (AF-CC) in younger paediatric patients with severe haemophilia A: Two open-label studies

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Introduction: The pharmacokinetics (PK), efficacy and safety of moroctocog alfa (AF-CC) have been demonstrated in haemophilia A patients aged ≥6 years.

Aim: These studies aimed to further describe moroctocog alfa (AF-CC) experience in paediatric patients (<12 years) with severe haemophilia A (FVIII:C < 1%).

Methods: Two prospective, open-label studies enrolled patients aged <12 years: one study with 37 previously treated patients (PTPs) and another with 23 previously untreated patients (PUPs). All patients initially received 50 IU/kg of moroctocog alfa (AF-CC) to evaluate either recovery alone, or with other PK parameters (6 to <12 years) before continuing treatment for 100 exposure days (EDs) or 24 months.

Results: At baseline, mean (±SD) recovery ranged between 1.32 ± 0.65 (PUPs aged <2 years) and 2.13 ± 0.82 (PTPs aged 6 to <12 years). The mean (±SD) half-life was 9.12 ± 1.94 hours in PTPs aged 6 to <12 years. No new safety signals were detected in either study, 2 transient lower titre inhibitors occurred in PTPs while 8 inhibitors (3 low and 5 high titre) were detected in PUPs. Most bleeding episodes resolved with one infusion (94% [893/954]). The annualised bleeding rate (ABR) in the PTP study was 27.5 and 4.2 for patients reporting an on-demand and routine prophylaxis regimen at baseline, respectively. In the PUP study, the overall ABR was 5.9.

Conclusion: Moroctocog alfa (AF-CC) had expected PK findings (lower recovery in young children compared with older children) along with being safe and efficacious in a population of young severe haemophilia A patients.

KEYWORDS
clinical trial, factor replacement, pharmacokinetics, previously treated patients, previously untreated patients, recombinant factor VIII

1 | INTRODUCTION

Moroctocog alfa, a B-domain-deleted rFVIII product initially licensed in 1998 in Europe and in 2000 in the United States (ReFacto; Wyeth Pharmaceuticals [Pfizer Inc]), originally contained human albumin. It has undergone reformulation to enhance its safety profile. The manufacturing process was changed to utilize an albumin-free cell culture (AF-CC), and a synthetic peptide affinity ligand (TN8.2) replaced the original murine monoclonal antibody used for

[†]Deceased.

affinity chromatography purification, and an additional 35 nm viral filtration step was added.[1,2] The new formulation, moroctocog alfa (AF-CC), under the brand name ReFacto AF in the European Union and other regions, and Xyntha in the United States, China, and other regions, is approved for treatment of patients with haemophilia A.[3,4]

Moroctocog alfa and moroctocog alfa (AF-CC) have demonstrated similar safety and efficacy profiles in previously treated patients (PTPs) aged ≥6 years.[2,5] Moroctocog alfa was also shown as safe and efficacious in previously untreated patients (PUPs) aged <1 to 52 months[6]; however, there are no published data on the safety or efficacy of moroctocog alfa (AF-CC) in PUPs of any age, or paediatric PTPs aged <6 years.

Moroctocog alfa (AF-CC) showed FVIII activity (FVIII:C) pharmacokinetics (PK) in PTPs aged 14 to 57 years bioequivalent to that observed after receiving either the original moroctocog alfa formulation or full-length rFVIII.[2] Data available for younger patients include Courter and Bedrosian's report of a mean recovery of 1.9 IU/dL/IU/kg in 46 PUPs aged 0 to 52 months who were treated with moroctocog alfa.[7] There are also simulations based upon a population PK model developed using data collected after administration of both moroctocog alfa and moroctocog alfa (AF-CC), which showed that young children require larger and more frequent doses to maintain similar trough FVIII:C as that observed in older children and adults.[8] Additional studies in young paediatric patients would be helpful to further understand these findings.

This paper describes results from two recently completed studies conducted in paediatric PUPs and PTPs (aged 0 to <12 years), as requested by the European Medicines Agency (EMA), to assess whether reformulation changed the FVIII:C PK, safety or efficacy of moroctocog alfa (AF-CC).

2 | MATERIALS AND METHODS

The studies were prospective, open-label studies of FVIII:C PK, efficacy and safety of moroctocog alfa (AF-CC) in paediatric patients <12 years of age based on the EMA guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products.[9] The PTP study was conducted from December 2009 through April 2016 at 27 centres in 11 European countries, and the PUP study was conducted from February 2010 through November 2016 at 35 centres in 12 European countries (Table S1). All parents/legal guardians provided written informed consent and patients provided assent for study participation (where applicable). The studies were conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines and local regulations.

The primary objective of the PTP study was to evaluate the PK and recovery of FVIII:C following moroctocog alfa (AF-CC) infusion. The secondary objectives were to evaluate the efficacy and safety of moroctocog alfa (AF-CC).

The primary objective of the PUP study was to evaluate the safety of moroctocog alfa (AF-CC), including the incidence of clinically significant inhibitors. The secondary objectives were to evaluate the FVIII:C recovery and the efficacy of moroctocog alfa (AF-CC).

2.1 | Patients

Both studies enrolled male patients with severe haemophilia A (FVIII:C < 1%). The PTP study enrolled patients with ≥50 exposure days (EDs) to any FVIII products (for patients <6 years of age) or with >150 EDs to any FVIII products (for patients 6 to <12 years of age), with no detectable inhibitors at study screening. The PUP study enrolled patients <6 years of age who were not previously treated with FVIII or blood products.

2.2 | Treatment

All patients began with a single 50-IU/kg infusion of moroctocog alfa (AF-CC) administered after a minimum 48-hour washout from any previous FVIII therapy. Patients were subsequently treated with a dose and frequency prescribed by each patient's treating physician, per local standard of care and in accordance with the Summary of Product Characteristics.[4] A written infusion log was kept by the patients or their parents/legal guardians to record the infusion days and the reason (prophylaxis, preventive or on-demand) for each infusion.

2.3 | Pharmacokinetic assessments

In the PTP study, in patients aged 6 to <12 years, blood samples were collected prior to and at 30 minutes and at 1, 3, 6, 9, 24, 28, 32 and 48 hours after the start of the study drug infusion at the enrolment visit (ED 1). For patients aged <6 years, as well as any older patients enrolled who did not participate in the extensive sampling, blood samples were collected only prior to and at 30 minutes after the start of the study drug infusion at ED1. For all patients, recovery was to be assessed at the 10 to 15 ED visit and the 50 ED visit. Thereafter, recovery studies were recommended, but were conducted at the discretion of the investigator at subsequent 6-month interval visits through the final visit (at study completion or upon early withdrawal). Recovery assessment in the PUP study was done at a frequency similar to that in the PTP study.

Samples collected were analysed at a central laboratory (Covance Laboratories, Inc.; Chantilly, VA, USA) for FVIII:C using a chromogenic substrate assay. The recovery was calculated as the ratio of the increase in FVIII:C observed (FVIII:C at 30 minutes after infusion − FVIII:C predose) to the dose administered and was expressed using units of IU/dL/IU/kg. Other PK parameters (for the patients with extensive sampling) were calculated using standard noncompartmental methods. Recovery and other parameters were summarized by age groups and ED within each study.

2.4 | Safety and efficacy

Following a screening period, all patients were to be followed for ≥50 EDs, with treatment ending after approximately 24 months from ED 1 or when patients had achieved approximately 100 EDs, whichever came first. A follow-up telephone call occurred 28 ± 10 days after the final study visit. Patients were evaluated on ED milestones of 10 to 15 EDs and of 50 EDs, as well as time-based visits at 6-month intervals for extended surveillance through 100 EDs (or 24 months, whichever occurred first), to monitor safety (including the development of FVIII inhibitors) and efficacy.

Safety and efficacy assessments were similar in both studies. For both protocols, samples for inhibitor testing were to be performed at ED 10-15, ED 50, along with visits at 6-month intervals and assayed at a central laboratory (Covance Laboratories, Inc.; Chantilly, VA, USA). Per EMA request and guidelines, clinically significant inhibitors were defined in the protocol as a central laboratory-confirmed positive inhibitor (≥0.6 Bethesda units [BU]/mL using the Nijmegen modification of the Bethesda assay present at 2 consecutive blood draws within a 6-week interval) and one 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 haemostatic products to achieve sufficient efficacy, or ≥2 bleeding events, indicating a decrease in the efficacy of the study drug. Factor VIII inhibitor levels were classified as low titre (0.6 to 5.0 BU/mL) and high titre (>5.0 BU/mL). Adverse events, as defined by the International Society on Thrombosis and Haemostasis,[10] were collected throughout the duration of the study.

Efficacy outcomes including the annualized bleeding rate (ABR), response to first on-demand infusion, the 4-point response scale and incidence of less-than-expected therapeutic effect (LETE) have definitions that have been described in detail previously.[5]

3 | RESULTS

3.1 | Patients

In total, 60 patients aged up to 12 years participated in the two studies. Thirty-seven patients participated in the PTP study: 18 were aged <6 years and 19 were aged 6 to <12 years. Thirty-five patients (94.6%) completed the study: one patient from each age cohort (<6 years and 6 to <12 years) withdrew prior to study completion. The reasons for withdrawal were parent/legal guardian request and protocol violation (did not meet inclusion/exclusion criteria). Patients in this study had a mean (± standard deviation [SD]) age of 6.5 ± 3.2 years and all patients were white, with the majority being of non-Hispanic and non-Latino ethnicity (Table 1).

In the PUP study, 23 patients participated and 19 completed the study. Reasons for discontinuation were per parent/legal guardian request (n = 1), for early discontinuation of the study by the sponsor (n = 1), and for FVIII inhibition (n = 2). Patients in this study had a mean (±SD) age of 1.0 ± 1.1 years, and the majority were white (95.7%) and of non-Hispanic and non-Latino ethnicity (95.7%) (Table 1).

TABLE 1 Patient demographics and baseline characteristics for both the PTP and PUP studies

Characteristic	PTPs <6 y (n = 18)	PTPs 6 to <12 y (n = 19)	Total PTPs (N = 37)	Total PUPs (N = 23)
Age, y				
N	18	19	37	23
Mean	3.6	9.2	6.5	1.0
SD	1.42	1.47	3.20	1.09
Median	4	10	6	0.6
Min, max	1, 5	6, 11	1, 11	0-5
Age category, n (%)				
0 to <28 d	0	0	0	0
28 days to <1 y	0	0	0	17 (73.9)
1 to <6 y	18 (100.0)	0	18 (48.6)	6 (26.1)
6 to <12 y	0	19 (100.0)	19 (51.4)	0
Sex, n (%)				
Male	18 (100.0)	19 (100.0)	37 (100.0)	23 (100.0)
Race, n (%)				
White	18 (100.0)	19 (100.0)	37 (100.0)	22 (95.7)
Other	0	0	0	1 (4.3)
Ethnicity, n (%)				
Hispanic or Latino	0	3 (15.8)	3 (8.1)	1 (4.3)
Non-Hispanic and non-Latino	18 (100.0)	16 (84.2)	34 (91.9)	22 (95.7)
Weight, kg				
N	18	19	37	22
Mean	17.4	36.6	27.3	9.7
SD	3.73	10.10	12.33	3.19
Median	17	40	22	9.6
Min, max	13, 29	20, 53	13, 53	4, 20

max, maximum; min, minimum; n, number of observations; N, number of patients in group; PTP, previously treated patient; PUP, previously untreated patient; SD, standard deviation.

3.2 | Treatment

In the PTP study, the overall mean (±SD) treatment interval duration was 421 ± 191 days. Those aged <6 years had a mean duration of 445 ± 186 days compared with 399 ± 197 days in the 6 to <12 year age cohort. The mean (±SD) and median (minimum, maximum) number of EDs during the study were 99 (±19) and 104 (2, 111), respectively. In this study, patients' treatment regimens were recorded at baseline as routine prophylaxis or on-demand, but patients were not required to remain on their baseline regimens throughout the study. The mean dose of moroctocog alfa (AF-CC), infused for any reason, for all PTP

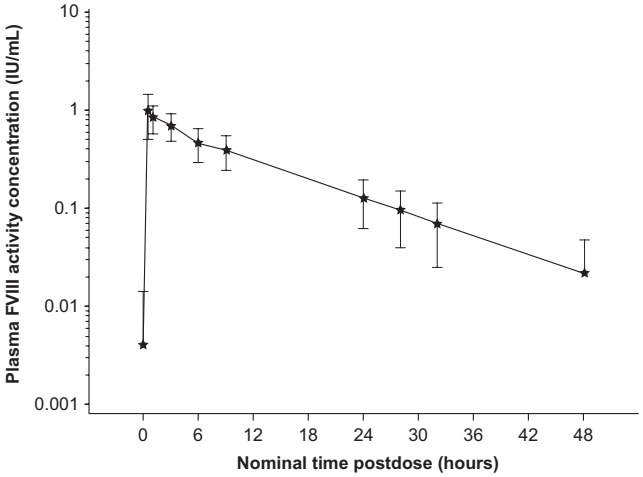

FIGURE 1 Mean (±SD) FVIII activity concentration vs time in previously treated patients patients aged 6 to 12 y

patients was 34 ± 9 IU/kg (n = 37). Regardless of reported regimen at baseline, the mean dose used for prophylaxis was 36 ± 9 IU/kg (n = 27) and the mean dose for on-demand treatment was 33 ± 9 IU/kg (n = 27).

In the PUP study, the overall mean (±SD) treatment interval duration was 520 ± 372 days. The mean (±SD) and median (minimum, maximum) EDs during the study were 81 ± 32 and 96 (8, 105), respectively. The mean dose infused for any non-recovery reason for all 23 PUP patients was 53 ± 34 IU/kg. The mean dose used for prophylactic infusion (22 patients) was 55 ± 34 IU/kg, while the mean dose used for on-demand treatment (21 patients) was 49 ± 26 IU/kg.

3.3 | Pharmacokinetics

The FVIII:C versus time curve for PTP patients aged 6 to <12 years is shown in Figure 1, and the PK parameters are shown in Table 2. The recovery observed in the PUP study is shown in Table 3.

3.4 | Efficacy

Efficacy data are presented in Table 4. Among the 60 paediatric patients who participated in the two studies, a total of 954 bleeding episodes were reported (804 in the PTP study, 150 in the PUP study). No incidents of LETE were reported for on-demand treatment of these bleeding episodes. In the prophylaxis setting, following a total of 4209 infusions (2457 in the PTP study, 1752 in the PUP study), a total of 4 incidents of LETE (2 from each study) were reported. Using the 4-point scale, 92.9% (97.8% in the PTP study, 66.4% in the PUP study) of first infusions for on-demand treatment of a bleeding episode were rated as "excellent" or "good." Overall, 93.6% (94.7% in the PTP study, 88.0% in the PUP study) of bleeding episodes resolved with a single on-demand infusion of moroctocog alfa (AF-CC). Although both studies reported ABRs, they were not designed to compare ABRs between the prophylaxis and on-demand regimens. The ABR data are presented in Table S2.

TABLE 2 Summary of factor VIII activity pharmacokinetic parameters for subjects aged 6 to <12 y in the PTP study

Parameter	Patients with data, N	PTPs 6 to <12 y (n = 19)*
C_{max}, IU/mL	19	0.9101 (45)
T_{max}, h	19	0.500 (0.467–3.030)
AUC_{inf}, IU h/mL	14	9.89 (41)
k_{el}, h^{-1}	14	0.07761 (22)
$t_{½}$, h	14	9.12 ± 1.94
MRT, h	14	12.80 (21)
CL, mL/h/kg	14	4.406 (30)
V_{ss}, mL/kg	14	56.42 (15)
Recovery, IU/dL/IU/kg	19	2.13 ± 0.822

AUC_{inf}, area under the plasma FVIII activity-time profile from time 0 extrapolated to infinity; CL, clearance; C_{max}, maximum plasma FVIII activity; k_{el}, terminal phase rate constant; MRT, mean residence time; PTP, previously treated patients; $t_{½}$, terminal elimination half-life; SD, standard deviation; T_{max}, time to C_{max}; V_{ss}, steady state volume of distribution.

N, number of patients contributing to the summary statistics. C_{max}, T_{max} and recovery include patients with samples only at predose and at 30 min after study drug administration.

*Geometric mean (geometric coefficient of variance) for all, except: median (range) for T_{max}; arithmetic mean ±SD for $t_{½}$ and recovery.

3.5 | Safety

3.5.1 | Inhibitors

In the PTP study, two patients had central laboratory-confirmed inhibitors that were both transient, low titre and without clinical manifestation. Of these 2, 1 patient had a positive inhibitor on two consecutive occasions prior to spontaneous resolution, and the other was an isolated finding. In addition, two other patients had positive inhibitor results at local laboratories that were not confirmed positive upon evaluation at the central laboratory. These inhibitors were also isolated/transient, low titre and without clinical sequelae. No patients developed inhibitors that met the protocol definition of clinically significant.

In the PUP study, a total of 8/23 patients (34.8%, 95% CI: 16.4, 57.3) had central laboratory-confirmed positive results for FVIII inhibitors (low-titre, n = 3; high-titre, n = 5). Two of the 8 were transient. Of the 8, four patients were observed to have inhibitors before reaching 20 EDs (on EDs 5, 11, 12 and 16) and 4 were observed between 20 and 50 EDs (on EDs 22, 24, 31 and 43). Of the subjects developing inhibitors after 20 EDs, 1 subject had received on-demand therapy along with intermittent prophylaxis, while 2 subjects had utilized once-weekly prophyalxis and 1 subject had administered 2-3 times/week prophylaxis. Of the 8 subjects with inhibitors, 3 did not fulfil the protocol definition of clinically significant inhibitor due to removal from the study prior to meeting the full EMA definition of inhibitor development.

TABLE 3 Summary of FVIII incremental recovery data [IU/dL]/[IU/kg] in the PUP study

Incremental Recovery	Statistics	Age Group	
		28 d to <24 Mo	2 to <6 y
ED 1	N	17	2
	Mean (SD)	1.32 (0.654)	1.76 (0.019)
	Min, max	0.0, 2.2	1.7, 1.8
ED 10-15	N	19	2
	Mean (SD)	1.26 (0.709)	0.82 (0.967)
	Min, max	0.0, 2.2	0.1, 1.5
ED 50	N	15	2
	Mean (SD)	1.64 (0.331)	1.65 (0.025)
	Min, max	1.0, 2.2	1.6, 1.7
Month 6	N	4	1
	Mean (SD)	1.44 (0.848)	1.22 (NA)
	Min, max	0.3, 2.3	1.2, 1.2
Month 12	N	4	0
	Mean (SD)	1.54 (0.984)	–
	Min, max	0.3, 2.7	–
Month 18	N	5	1
	Mean (SD)	1.19 (0.606)	2.05 (NA)
	Min, max	0.4, 1.7	2.1, 2.1
Final visit	N	17	2
	Mean (SD)	1.30 (0.698)	1.52 (0.124)
	Min, max	0.0, 2.2	1.4, 1.6

ED, exposure day; max, maximum; min, minimum; PUP, previously untreated patient; SD, standard deviation.

TABLE 4 Efficacy data for both the PTP and PUP studies

Parameter	PTP Study (n = 37)	PUP Study (n = 23)	Total (N = 60)
Bleeding events resolved with 1 dose, % (no./total)	95 (761/804)	88 (132/150)	94 (893/954)
Excellent/good response to first infusion, % (no./total)	98 (786/804)	66 (99/149*)	93 (885/953)
LETE, on-demand, % (no./total)	0.0 (0/804)	0.0 (0/150)	0.0 (0/954)
LETE, prophylaxis, % (no./total)	0.08 (2/2457)	0.11 (2/1752)	0.10 (4/4209)

LETE, less-than-expected therapeutic effect; PTP, previously treated patient; PUP, previously untreated patient.

*One patient with a response of "good" recorded the infusion reason as "prophylaxis" rather than "on-demand" and was not counted in the total number of bleeding events for this analysis; thus, the total number of bleeding episodes for this analysis was 149.

3.6 | Adverse events

Between the two studies, 80% of subjects reported at least 1 treatment-emergent adverse event (28 [75.7%] PTPs; 20 (87.0%) PUPs). Treatment-emergent AEs occurring in more than 5% of patients in either study are listed in Table S3. Not including inhibitors, 20 serious adverse events (SAEs) were reported between the two studies (7 in the PTP study; 13 in the PUP study). None of these events were considered related to the study drug. Notably, no episodes of allergic reaction to the study drug occurred in either study.

4 | DISCUSSION

The ability to replace deficient and/or inactive coagulation factors remains the primary treatment modality for most patients.[11] The efficacy of recombinant products has been demonstrated in both adult and paediatric patients. These products lower the ABR when administered for prophylaxis and are effective at treating acute bleeding events in the on-demand setting. When started at a young age, prophylactic administration of an rFVIII product may preserve joint function and retard joint damage.[12,13] Moroctocog alfa (AF-CC) has been shown in PTPs with haemophilia A aged

≥6 years of age to be efficacious for both prophylaxis (through reduction of the ABR) and on-demand treatment (as shown by infrequent LETE and complete resolution of bleeding episodes with 1 or 2 infusions).[2,5]

The recovery and PK parameter values observed in these studies were similar to what has been reported by others for children with haemophilia A of this age for moroctocog alfa,[7,14] as well as for other FVIII replacement products that are not in the extended half-life class.[15,16] Blanchette and colleagues reported mean ±SD half-life of 9.9 ± 1.9 hours and recovery of 1.9 ± 0.4 IU/dL/IU/kg in 47 children after treatment with rurioctocog alfa. At baseline, the children had a mean ±SD age of 3.1 ± 1.5 years and ≥50 EDs.[17] Barnes et al reported a mean (min, max) half-life of 10.7 (7.8, 15.3) hours and recovery of 1.9 (1.3–2.8) IU/dL/IU/kg in 20 children (mean age, 12.8 years) after treatment with octocog alfa.[18]

No new safety signals emerged in either study. In the PTP study, the frequency of central laboratory-confirmed inhibitors was similar to that seen in other studies with moroctocog alfa and moroctocog alfa (AF-CC).[2,5] All were low titre and transient, with only one inhibitor being detected on more than one occasion which calls into question the significance of these laboratory findings. In the PUP study, the overall rate of inhibitor development is similar to that seen with moroctocog alfa.[6] Because of the relatively low number of patients enrolled in the PUP study and inherent differences in study design and methodology, a direct comparison cannot be made with other studies, including the recently reported Survey of Inhibitors in Plasma-Product Exposed Toddlers (SIPPET) study.[19] Notably, only 7 patients in SIPPET used moroctocog alfa (AF-CC), making interpretation difficult.

Both the PTP and PUP studies addressed the efficacy of on-demand treatments. Moroctocog alfa (AF-CC) was shown to be efficacious in achieving haemostasis in the setting of acute bleeding episodes in paediatric PTPs and PUPs. The LETE rates for routine prophylaxis and on-demand settings in both studies were consistent with those reported previously in an older cohort of patients with moroctocog alfa (AF-CC).[2] While the first infusion was rated as excellent/good in 93% of bleeding events among the 60 paediatric patients, we noted that only 66% of first infusions in the PUP study were rated as good or excellent. This number is discrepant with the finding that 88% of these bleeding events were treated with a single infusion of moroctocog alfa (AF-CC) and 97% were treated with no more than two infusions. However, 13% of the bleeding events were classified as "data not reported," and that may have contributed in part to this inconsistency. Neither study was designed to compare ABR between prophylactic and on-demand use. As such, patients were able to move between treatment regimens during the course of their participation in the study, and this should be considered when interpreting the ABRs. Specifically, the frequency of prophylaxis in both studies ranged from once daily to once weekly with many subjects modifying frequency during the study and some utilizing on-demand intermittently. However, in the PTP study, when looking at patients who reported prophylactic infusions versus those reporting only on-demand infusions, the ABR is lower for the patients reporting prophylaxis, similar to that seen in other studies with moroctocog alfa and moroctocog alfa (AF-CC) (Table S1).[2,5,6] In the PUP study, ABR was calculated for the entire group and no analysis was performed based on regimen. However, it is interesting to note that when looking at reported infusions, only 1 of the 23 patients used exclusively on-demand treatments. Overall, the efficacy results from these studies are consistent with those seen in prior studies of previously treated adults and children aged ≥6 years who received moroctocog alfa (AF-CC),[2,5] and in PUPs who received moroctocog alfa,[6] supporting the finding that moroctocog alfa (AF-CC) is efficacious in treating paediatric patients with haemophilia A. Finally, when efficacy data were analysed post hoc by age group in the PTP study (0 to <6 years and 6 to <12 years), no discernible difference was found (data not shown).

Taken together, findings from these two studies were consistent with those of studies conducted with the predecessor product (moroctocog alfa), and support the safety and efficacy of moroctocog alfa (AF-CC) in PTP and PUP paediatric patients with haemophilia A.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

J. Korth-Bradley, F. Huard, P. Rendo and L. Smith contributed to the study design. L. Rusen and K. Kavakli served as study investigators and enrolled patients. J. Korth-Bradley, F. Huard, P. Rendo, J. Fuiman, J. Baumann, L. Smith, C. Alvey and J. Rupon participated in the collection and assembly of data and in data analysis. All authors had full access to the data and contributed to the drafting, critical review, and revision of the manuscript. All authors granted approval of the final manuscript for submission.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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