

Clinical Pharmacology Review (9/19/2007) – XYNTHA

STN125264

Sponsor: Wyeth Research

Product: ReFacto Albumin Free (AF), Antihemophilic Factor VIII, moroctocog alfa, B-Domain

Deleted recombinant Factor VIII (BDDrFVIII)

Indication: For hemophilia A

Date Received: April 22, 2007

Reviewer: Iftekhar Mahmood, Ph. D.

RPM: Pauline Cottrell

Through: Basil Golding, M.D.

Date: September 19, 2007

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INTRODUCTION

ReFacto (moroctocog alfa) is a B-domain deleted recombinant factor VIII (BDDrFVIII) product manufactured by Wyeth. It is licensed for use in patients with hemophilia A. Moroctocog alfa manufactured using an albumin-free cell culture (moroctocog alfa [AF-CC]) is a potential successor to ReFacto. While moroctocog alfa (AF-CC) is manufactured through a process that has been modified, the structure of moroctocog alfa (AF-CC) is comparable to ReFacto. The moroctocog alfa (AF-CC) modified process used the ----- for manufacture of ReFacto to generate a ----- and removed the use of human serum albumin in the cell culture process. The purification process has been further refined to purify BDDrFVIII via a column chromatography method that employs a chemically synthesized affinity ligand (TN8.2), replacing the murine monoclonal antibody sepharose resin. This thereby eliminates a potential risk of

viral contamination associated with the murine monoclonal antibody and its manufacture. In addition, a virus-retaining -----, expanding upon the comprehensive multifaceted viral safety program currently in place for ReFacto. The net result of these modifications further improves upon the overall viral safety of ReFacto.

Wyeth has conducted a study to examine the pharmacokinetic (PK) properties of moroctocog alfa (AF-CC) manufactured with the aforementioned modifications to the manufacturing process in place, as well as to establish the efficacy and safety of the drug product. Moroctocog alfa (AF-CC) is also referred to as ReFacto AF.

2 Pages Determined

to be not releasable

FINAL CLINICAL PHARMACOLOGY LABELING

RECOMMENDATION

From pharmacokinetics perspective, this study is acceptable.

Iftekhar Mahmood, Ph. D.
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Division of Hematology, OBRR
Date: September 19, 2007

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Study Title: A randomized two-way blinded crossover-design study to establish the bioequivalence of B-domain deleted recombinant factor VIII (BDDrFVIII, moroctocog alfa [AF-CC]) with a full-length recombinant factor VIII preparation (FLrFVIII, Advate), followed by an open-label trial of the safety and efficacy of moroctocog alfa (AF-CC) in previously treated patients with hemophilia A.

OBJECTIVES

The primary safety objective of this study was to determine the incidence rate of FVIII inhibitors associated with the use of moroctocog alfa (AF-CC) in the study patient population. The primary efficacy objective of this study was to establish the bioequivalence of moroctocog alfa (AF-CC) and a full-length recombinant FVIII (Advate) using the OS FVIII assay.

One of the secondary objectives of this study was to characterize the PK of moroctocog alfa (AF-CC) in comparison to Advate.

STUDY DESIGN

The study consisted of 2 parts, a PK period and a safety and efficacy (SE) period. The SE period of the study was conducted as an open-label, multicenter trial of moroctocog alfa (AF-CC) in routine prophylaxis and on-demand therapy in at least 81 previously treated patients (PTPs) with severe or moderately severe hemophilia A.

In addition to the SE period of the trial, 31 patients participated in a double-blind crossover study comparing the PK of moroctocog alfa (AF-CC) to Advate. This crossover PK assessment occurred at the beginning of the study. After completing the crossover PK study these patients entered in the SE period of the trial. Approximately 6 months later, all PK patients participated in the 6-month follow-up PK assessment with moroctocog alfa (AF-CC), at the end of the SE period and before the conclusion of the study. This 6-month follow-up PK assessed the stability of the moroctocog alfa (AF-CC) PK response over time. The PK assessments made at visits 2 and 3 for those patients participating in the PK period of the trial are referred to as PK1 and PK2, respectively. PK3 (visit 11) refers to the final, 6-month infusion of 50 IU/kg of moroctocog alfa (AF-CC), which coincided with the final safety and efficacy visit (study visit 10).

Thirty one patients were randomized 1:1 to receive a sequence of a single infusion of moroctocog alfa (AF-CC) followed by Advate or a single infusion of Advate followed by moroctocog alfa (AF-CC). The mean age of the patients (n = 31, all males) was 27.1 years (range: 14-57 years). There were 4 children ages 12 to 16 years in the study. The patients received 50 IU/kg single dose infusions of moroctocog alfa (AF-CC) and Advate, respectively. The sequence of these 2 infusions was randomized. Both infusions were to occur within 28 days of each other. There was a minimum of a 72-hour washout period before all PK infusions. The patients returned after approximately 6 months of treatment at the end of the SE period of the trial (at study visit 11) to receive an infusion of 50 IU/kg of moroctocog alfa (AF-CC) for a final PK assessment. Blood samples were collected at 0.25, 0.5, 1, 3, 6, 9, 24, 28, 32, and 48 hours. Total blood volume collected for each PK assessment was slightly less than or approximately 100 mL.

ANALYTICAL METHODS

Factor VIII Activity:

Individual patient plasma FVIII concentrations were quantified using a validated one

stage (OS) FVIII activity clotting assay (Activated Partial Thromboplastin Time, or aPTT) with ---- Plasma Standard Calibrators.

Inhibitor Assay:

Assessment of the presence of neutralizing antibodies against FVIII (inhibitors) was performed using the Nijmegen modification of the Bethesda inhibitor assay (BIA) and a normal plasma test-base and reported in Bethesda Units (BU). The criterion for a positive test result was ≥ 0.6 BU/mL. Values ---- BU/mL, the lower limit of quantitation for this assay, were reported as 0.0 BU/mL. Plasma samples that had a positive inhibitor titer by the Nijmegen modification of the BIA were then tested further using a normal plasma test-base and a moroctocog alfa (AF-CC) test-base.

Anti-Moroctocog Alfa (AF-CC) Assay:

Patient serum samples were tested for the development of antibodies (both neutralizing and non-neutralizing) to moroctocog alfa (AF-CC) using a validated ELISA. A positive immune response was thus defined as an AI that exceeds the cutoff value ($AI > 2.34$) coupled with a significant increase in AI (defined as $RI > 2$).

Anti-CHO Assay:

Patient serum samples were tested for the development of antibodies to CHO cell proteins derived from the cell line used in manufacturing of moroctocog alfa (AF-CC) using a validated ELISA. An immune response to CHO was defined as a high-titer AI (> 5.57) coupled with a significant increase in AI ($RI > 2$).

Anti-TN8.2 Assay:

Patient serum samples were tested for the development of antibodies to TN8.2, the affinity ligand used in purification of moroctocog alfa (AF-CC), using a validated ELISA. A sample was considered negative if the log titer is < 1.70 and positive if it is ≥ 1.70 .

Moroctocog Alfa (AF-CC) and Advate Actual Dose Calculation:

The PK1 and PK2 assessments were performed in a blinded manner, while the PK3 assessment was open-label. The manufacturer's actual labeled potency that was used to calculate patient dosing was determined by the respective manufacturer using a concentrate standard. To align the FVIII:C values obtained for patient samples assayed at the central laboratory and the administered doses of the 2 drugs, the potency of each lot used in the PK calculations was determined head-to-head using the same OS assay by the central laboratory ----- . The OS assay used at the central laboratory was the same assay used for assessment of patient samples, and this assay was referenced to a common, commercially available, normal plasma standard, ---- Standard Human Plasma ----- . As specified *a priori*, for the purposes of the primary bioequivalence analysis, the actual doses administered during the PK assessments were determined based on the potency as determined by the central laboratory. The actual dose was also calculated based on the manufacturer's labeled potency for supplemental PK analyses. During the PK assessments, moroctocog alfa (AF-CC) and Advate vials were reconstituted with a dilution solution by an unblinded pharmacist and were administered (50 IU/kg) based on the manufacturer's labeled potency (for a given lot). The total

volume administered was recorded on the CRFs. The actual dose (IU) administered during the PK assessments (PK1, 2, and 3) was calculated using the product of [the potency (IU) as determined by the central laboratory potency assessment or the manufacturer's labeled potency (for a given lot number) divided by dilution factor (total diluent volume used to reconstitute each vial of the respective PK drug. Recommended volumes were 4 mL and 5 mL for moroctocog alfa (AF-CC) and Advate vials, respectively.

Factor VIII Concentrations:

All reported FVIII:C values were calculated from at least 2 different dilutions. The FVIII analytical laboratory reported a total of 987 FVIII:C values for the 32 patients who participated in at least 1 PK assessment. When all reported FVIII:C values were plotted against time for visual inspection, it appeared that the vast majority of these evaluated means were at or very close to the respective value expected from the FVIII concentration-versus-time profile; however, some FVIII:C values appeared to be aberrant. To make use of the information from these aberrant values but balance their contribution to any given concentration-versus-time profile, it was decided that FVIII:C values that were not within 50% of the mean of the preceding and proceeding time values were to be retested. Based on this rule, there were 39 (<4%) FVIII:C values that were retested and the results for the repeated analysis were reported. The PK analysis was based on the final reported FVIII:C values and no FVIII:C values were excluded from the analysis.

Concentration Adjustment and Inclusion or Exclusion of Subjects in PK Analysis

All FVIII concentrations were adjusted for their pre-infusion (time = 0 h) FVIII:C level and normalized for dose (50 IU/kg, based on the central laboratory potency assessment) before the PK and recovery calculations. Similar rules were applied to obtain FVIII concentrations based on the manufacturer's labeled potency, for additional PK analysis.

Of the total 31 patients randomized to participate in the PK assessments, 4 patients had a measurable ($\geq 1\%$, 0.01 IU/mL) pre-infusion FVIII:C (min: 0.0100, max: 0.0107 IU/mL) prior to Advate treatment; 1 patient had a measurable pre-infusion level (0.0127 IU/mL) prior to his first moroctocog alfa treatment; and 13 patients had measurable pre-infusion levels (min: 0.101; max: 0.6787 IU/mL) at month 6 PK (prior to their second moroctocog alfa PK treatment). Any of the FVIII concentrations resulting in negative values after subtracting for pre-infusion FVIII:C level were regarded as missing (as was the case for patient -----, PK3 at 28 and 48 hours; patient -----, PK3 at all time points except 0.25 and 3 hours; patient -----, PK3 at 48 hours; and patient -----, PK3 at 48 hours).

Thirty-two (32) patients received at least 1 PK dose. Thirty-one (31) patients completed both the first (PK1) and the second (PK2) assessments. Patient -----, who was randomized to the SE period but received a PK1 dose in error, did not complete the PK2 assessment. Thirty (30) patients completed PK1 and PK2 assessments and were included in the bioequivalence evaluation. Patient ----- was excluded because 4 of his 11 samples (at 0.25, 0.5, 1, and 6 hours) after the Advate infusion had thawed before

reaching the central laboratory and could not be analyzed, compromising the evaluation of this PK assessment.

Twenty-seven (27) of 31 patients who completed the PK1 and PK2 assessments for bioequivalence testing also completed the PK3 assessment at month 6. Four (4) patients who completed the PK1 and PK2 assessments did not complete the PK3 assessment, including:

- Patient -----: This patient did not participate in PK3 at the investigator's discretion, as the patient had bleeds that required treatment during FVIII washout attempts.
- Patient -----: This patient could not complete the PK3 assessment because of scheduling constraints.
- Patient -----: This patient did not complete the PK3 assessment at the investigator's discretion. He twice attempted to coordinate the PK3 assessment in conjunction with visit 10, but was not successful. The investigator ultimately decided to complete visit 10, after which the patient began using his regular FVIII replacement therapy, and no further plans were made for completing the PK3 assessment.
- Patient -----: This patient did not complete the PK3 assessment at Wyeth's discretion. After the PK2 assessment, the sponsor was informed that the dose administered for the PK2 assessment had infused into the soft tissue of the arm rather than into the vein. Wyeth decided to discontinue this patient from further PK assessments at PK3 (visit 11). After unblinding the study, there was no evidence that the administration of test article at the PK2 visit had compromised his PK analysis, and this patient's PK2 data is included in the analysis of bioequivalence.

RESULTS

Pharmacokinetic Results Based on Central Laboratory Potency Assessment:

Plasma FVIII:C concentrations increased sharply after IV infusion of either moroctocog alfa (AF-CC) or Advate. After the end of the infusion, the decline of FVIII:C exhibited biphasic disposition. The elimination half-life of AF-CC and Advate was 11.2 ± 5.0 and 13.3 ± 5.8 hours, respectively. The clearance of AF-CC and Advate was 4.08 ± 1.89 and 3.55 ± 1.48 mL/hr/kg, respectively. The 90% confidence interval on log transformed C_{max} and $AUC_{(0-\infty)}$ was 92.5 to 108.3% 81.6 to 94.8%, respectively, indicating that the products are pharmacokinetically equivalent. The PK parameters of moroctocog alfa and Advate are summarized in Table 1. Concentrations vs time plots of moroctocog alfa and Advate are shown in Figure 1.

TABLE 1

PK parameters for Moroctocog Alfa and Advate in Previously Treated Patients With Hemophilia A (Based on Central Laboratory Potency Assessment)

Treatment	C _{max} (IU/mL)	AUC _t (IU·hr/mL)	AUC _∞ (IU·hr/mL)	t _{1/2} (hr)	K-value (IU/dL per IU/kg)	In vivo Recovery (%)
Advate						
Mean ± SD	1.19 ± 0.32	15.0 ± 5.4	16.5 ± 6.3	13.3 ± 5.8	2.39 ± 0.65	114 ± 30
(Min, Max)	(0.64, 2.06)	(6.5, 24.2)	(7.5, 26.7)	(5.9, 31.2)	(1.28, 4.13)	(59.7, 200)
n	30	30	30	30	30	30
Moroctocog alfa (AF-CC)						
Mean ± SD	1.17 ± 0.23	13.8 ± 5.7	14.7 ± 6.1	11.2 ± 5.0	2.35 ± 0.47	112 ± 22
(Min, Max)	(0.66, 1.62)	(4.8, 27.1)	(5.4, 28.7)	(3.5, 33.9)	(1.32, 3.25)	(60.7, 152)
n	30	30	30	30	30	30
Ratios of geometric LS means and 90% confidence intervals ^a						
Ratio of geometric LS means	-	89.8%	88.0%	-	100%	-
90% Log- transformed CI	-	83.3% - 96.9%	81.6% - 94.8%	-	92.5% - 108%	-

Moroctocog Alfa (AF-CC) PK Results at Baseline versus Month 6 (PK3): Central Laboratory Potency Assessment:

The PK parameters based on the central laboratory potency assessment for the 25 patients are presented in Table 2. The PK parameters were comparable at baseline and month 6. Concentrations vs time plots of moroctocog alfa at baseline and month 6 are shown in Figure 2. The 90% confidence interval on log transformed C_{max} and AUC_(0-∞) remained within 80% to 125%.

Figure 1 Mean (± SE) Plasma FVIII:C Versus Time Profiles for Moroctocog Alfa and Advate (Based on Central Laboratory Potency Assessment)

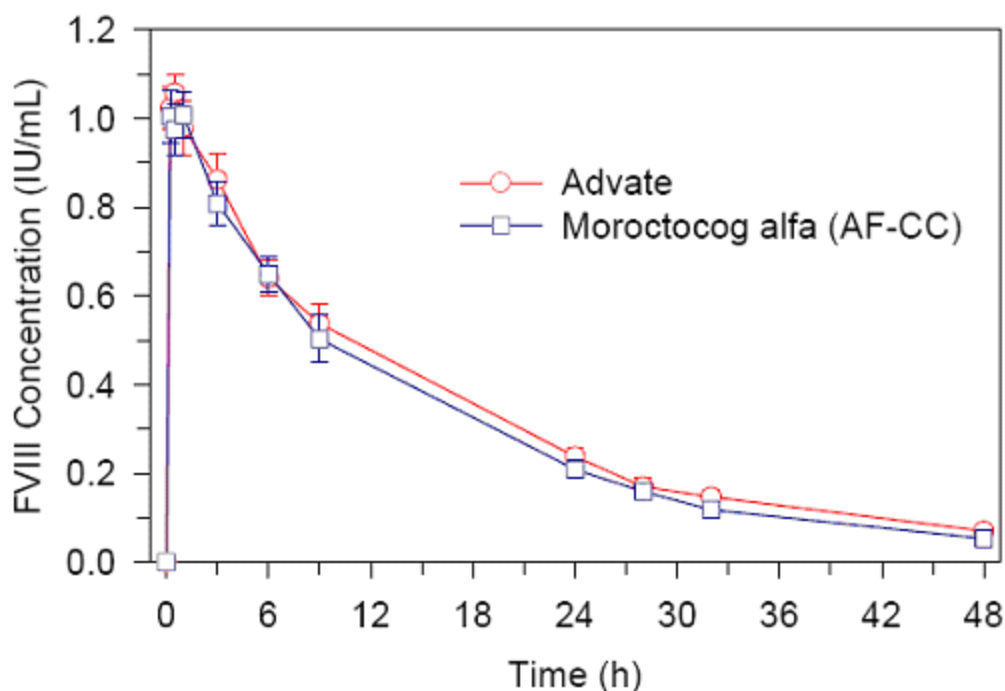
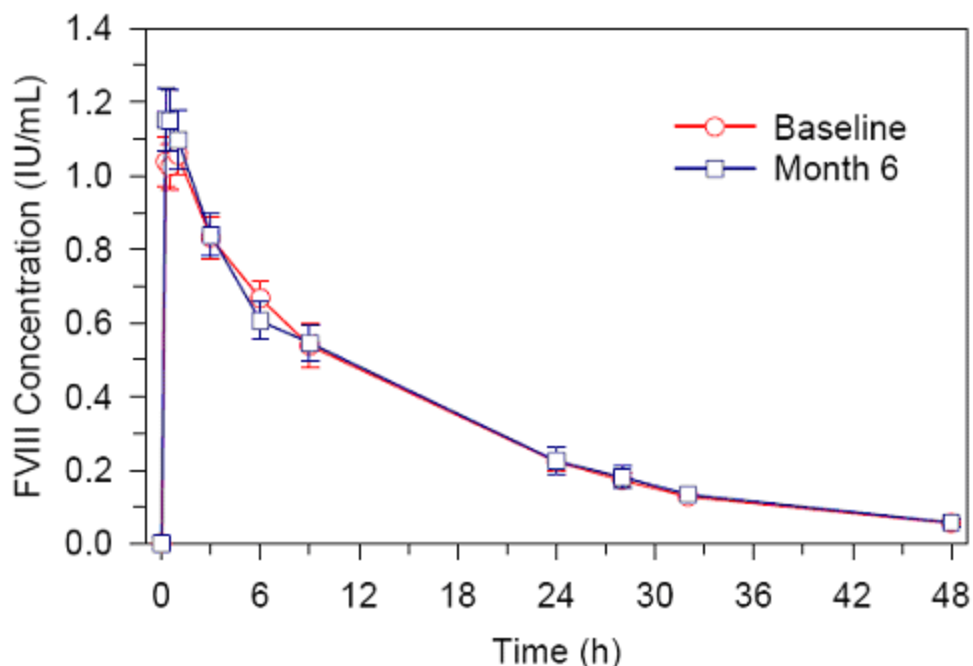


TABLE 2
PK parameters for Moroctocog Alfa at baseline and month 6 in Previously Treated Patients With Hemophilia A (Based on Central Laboratory Potency Assessment)

Visit	C _{max} (IU/mL)	AUC _t (IU·hr/mL)	AUC _∞ (IU·hr/mL)	t _{1/2} (hr)	K-value (IU/dL per IU/kg)	In vivo Recovery (%)
Baseline						
Mean ± SD	1.22 ± 0.21	14.6 ± 5.8	15.5 ± 6.1	11.8 ± 5.1	2.45 ± 0.42	116 ± 21
(Min, Max)	(0.68, 1.62)	(4.8, 27.1)	(5.4, 28.7)	(6.4, 33.9)	(1.36, 3.25)	(61.4, 152)
n	25	25	25	25	25	25
Month 6						
Mean ± SD	1.34 ± 0.44	14.4 ± 6.6	16.2 ± 7.6	14.3 ± 14.1 ^a	2.69 ± 0.87	126 ± 41
(Min, Max)	(0.74, 2.53)	(5.8, 40.0)	(6.1, 40.9)	(5.8, 75.7)	(1.49, 5.06)	(68.2, 249)
n	25	25	25	25	25	25
Ratios of geometric LS means and 90% confidence intervals ^b						
Ratio of geometric LS means	-	99.4%	103%	-	107%	-
90% Log-transformed CI	-	88.7% - 111%	93.3% - 115%	-	95.7% - 119%	-

Figure 2
Mean (± SE) Plasma FVIII:C Versus Time Profiles for Moroctocog Alfa at baseline and month 6 (Based on Central Laboratory Potency Assessment)



Pharmacokinetic Results Based on Manufacturer's Labeled Potency:

The sponsor did another PK analysis based on manufacturer's labeled potency. The elimination half-life of AF-CC and Advate was 11.2 ± 5.0 and 13.3 ± 5.8 hours, respectively. The clearance of AF-CC and Advate was 4.51 ± 2.23 and 4.94 ± 2.13 mL/hr/kg, respectively. The 90% confidence interval on log transformed C_{\max} and $AUC_{(0-\infty)}$ was 117 to 138% and 103 to 122%, respectively. The PK parameters of moroctocog alfa and Advate are summarized in Table 3. Concentrations vs time plots of moroctocog alfa and Advate are shown in Figure 3.

There appears to be some difference in the PK parameters calculated based on manufacturer's labeled potency. Both C_{\max} and $AUC_{(0-\infty)}$ are lower based on manufacturer's labeled potency than central laboratory potency. The 90% confidence interval for C_{\max} based on manufacturer's labeled potency is outside of 80% to 125% (based on central laboratory potency, the C_{\max} was within 80% to 125%).

Moroctocog alfa (AF-CC) PK Results at Baseline versus Month 6 (PK3): Manufacturer's Potency Assesment:

The PK parameters based on manufacturer's potency assessment for the 25 patients are presented in Table 4. The PK parameters were comparable at baseline and month 6. Concentrations vs time plots of moroctocog alfa at baseline and month 6 are shown in Figure 4. The 90% confidence interval on log transformed C_{\max} and $AUC_{(0-8)}$ remained within 80% to 125%.

TABLE 3

PK parameters for Moroctocog Alfa and Advate in Previously Treated Patients

With Hemophilia A (Based on Manufacturer's Labeled Potency)

Treatment	C _{max} (IU/mL)	AUC _t (IU·hr/mL)	AUC _∞ (IU·hr/mL)	t _{1/2} (hr)	K-value (IU/dL per IU/kg)	In vivo Recovery (%)
Advate						
Mean ± SD	0.86 ± 0.24	10.8 ± 3.8	11.9 ± 4.5	13.3 ± 5.8	1.72 ± 0.47	82.2 ± 21.5
(Min, Max)	(0.52, 1.42)	(4.5, 17.3)	(5.2, 19.0)	(5.9, 31.2)	(1.04, 2.84)	(49.2, 137)
n	30	30	30	30	30	30
Moroctocog alfa (AF-CC)						
Mean ± SD	1.08 ± 0.22	12.7 ± 5.2	13.5 ± 5.6	11.2 ± 5.0	2.15 ± 0.44	103 ± 21
(Min, Max)	(0.58, 1.41)	(4.1, 23.6)	(4.7, 25.0)	(3.5, 33.9)	(1.15, 2.83)	(52.8, 132)
n	30	30	30	30	30	30
Ratios of geometric LS means and 90% confidence intervals ^a						
Ratio of geometric LS means	-	114%	112%	-	127%	-
90% Log-transformed CI	-	105% - 124%	103% - 122%	-	117% - 138%	-

Figure 3
Mean (± SE) Plasma FVIII:C Versus Time Profiles for Moroctocog Alfa and Advate (Based on Manufacturer's Labeled Potency)

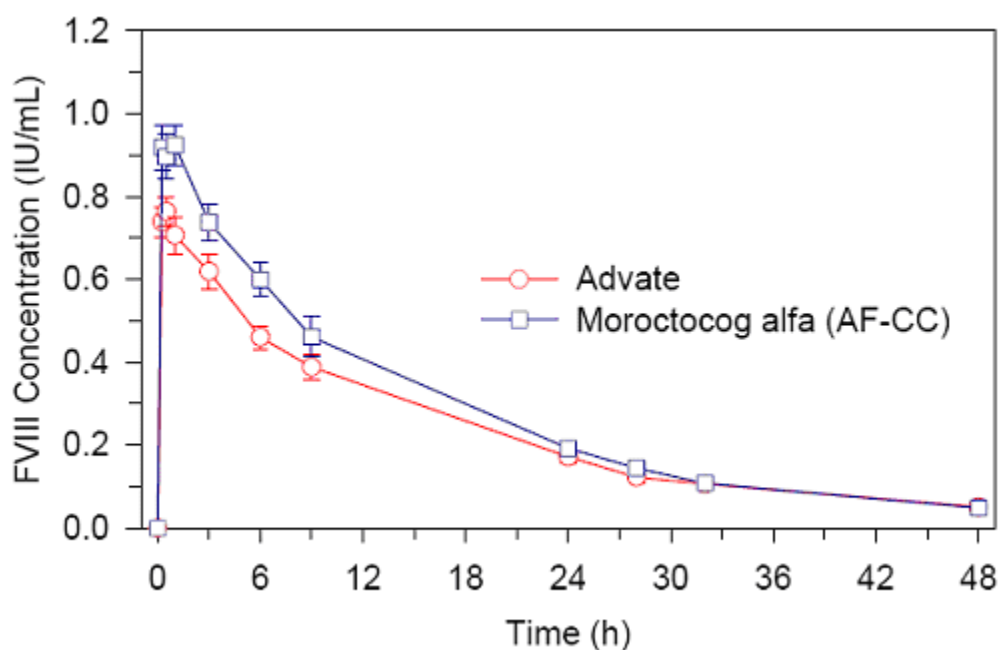


TABLE 4
PK parameters for Moroctocog Alfa at baseline and month 6 in Previously Treated Patients With Hemophilia A (Based on Manufacturer's Potency Assessment)

Parameters	C _{max} (IU/mL)	AUC _(0-inf)	Half-life (hrs)	K-value	% Recovery
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N	25	25	25	25	25
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Baseline:

Mean ± SD	1.12 ± 0.19	14.2 ± 5.5	11.8 ± 5.1	2.23 ± 0.39	105.5 ± 19.4
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Range	0.593 - 1.413	4.7 – 25.0	6.4 – 33.9	1.19 – 2.83	53.4 – 132.0
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90% CI

Month 6:

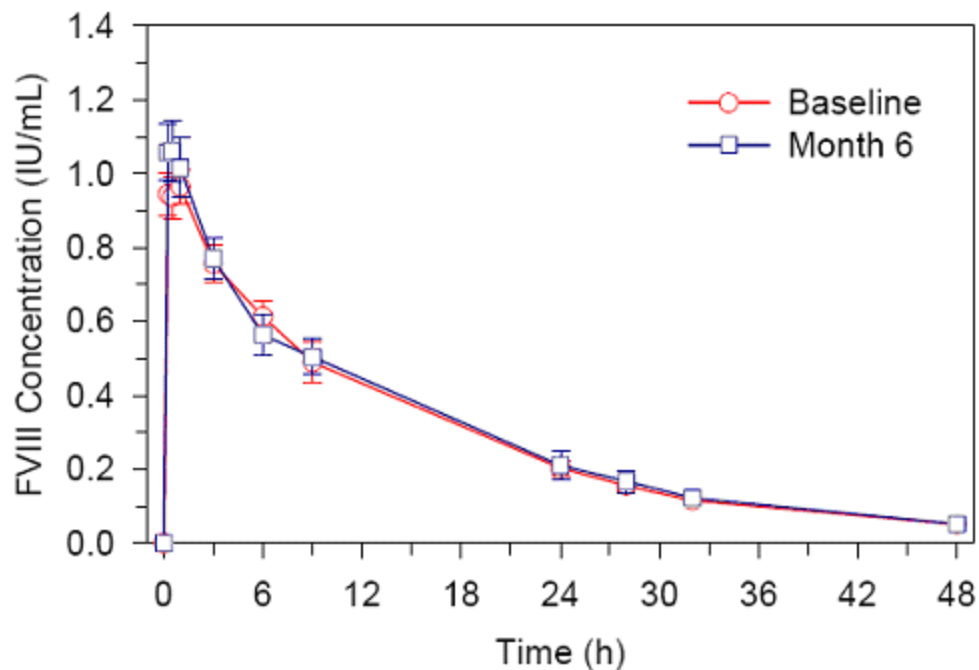
Mean ± SD	1.24 ± 0.42	15.0 ±7.5	14.3 ± 14.1	2.47 ± 0.84	115.8 ± 39.9
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Range	0.647 - 2.598	5.3 – 42.0	5.8 – 75.7	1.29 – 5.20	59.3 – 255.9
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90% CI	96.4 – 119.59	93.88 – 115.37
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Units: AUC_(0-inf) = IU*hr/mL; K-value: (IU/dL)/(IU/kg)

Figure 4
Mean (± SE) Plasma FVIII:C Versus Time Profiles for Moroctocog Alfa at baseline and month 6 (Based on Manufacturer's Potency Assessment)



CONCLUSIONS

Based on the central laboratory potency assessment, the PK parameters of moroctocog alfa and Advate were comparable. The 90% confidence interval for C_{max} and $AUC_{(0-\infty)}$ were within 80% to 125%, indicating that the two products are pharmacokinetically equivalent. The PK profiles of moroctocog alfa at baseline and month 6 were similar. The 90% confidence interval for C_{max} and $AUC_{(0-\infty)}$ of moroctocog alfa (AF-CC) at baseline and month 6 were also within 80% to 125%.

Based on the manufacturer's labeled potency, Advate showed approximately 27% lower peak FVIII:C and recovery compared to moroctocog alfa (AF-CC). However, 90% confidence interval for C_{max} and $AUC_{(0-\infty)}$ were within 80% to 125%, indicating that the two products are pharmacokinetically equivalent. Furthermore, the PK profiles of moroctocog alfa at baseline and month 6 were similar and pharmacokinetically bioequivalent.