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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: ReFacto AF® / Moroctocog alfa (AF-CC)

PROTOCOL NO.: 3082B2-310-WW (B1831070)

PROTOCOL TITLE: A Randomized Two-way Blinded Crossover-Design Study to Establish the Bioequivalence of B-Domain Deleted Recombinant Factor VIII (BDDrFVIII, ReFacto AF) With a Full-Length Recombinant Factor VIII Preparation (FLrFVIII, Advate), Followed by an Open-Label Trial of the Safety and Efficacy of ReFacto AF in Previously Treated Patients With Hemophilia A

Study Centers: Twenty-five (25) centers took part in the study and randomized subjects; 12 in the United States, 3 in Poland, 2 each in New Zealand and Sweden, 1 each in Hungary, Finland, Italy, Belgium, Germany, and Australia.

Study Initiation and Final Completion Dates: June 2005 to November 2006.

Phase of Development: Phase 3

Study Objectives:

Primary Objective:

- The primary safety objective of this study was to determine the incidence rate of Factor VIII (FVIII) inhibitors associated with the use of moroctocog alfa albumin-free cell culture (AF-CC) in the study subject population. The primary efficacy objective of this study was to establish the bioequivalence of moroctocog alfa (AF-CC) and a FLrFVIII using the one stage (OS) FVIII assay.

Secondary Objectives:

- To characterize the pharmacokinetics (PK) of moroctocog alfa (AF-CC) in comparison to FLrFVIII and over time;
- To characterize the efficacy of moroctocog alfa (AF-CC) in preventing and treating bleeding episodes during prophylaxis treatment;
- To characterize the efficacy response of both prophylactic and on-demand infusions of moroctocog alfa (AF-CC);

- To characterize the rate of "Less than Expected Therapeutic Effect" (LETE) responses of moroctocog alfa (AF-CC) when used either prophylactically or for treatment of a bleeding episode ("on-demand") or in the instance of low recovery;
- To characterize the consumption of moroctocog alfa (AF-CC) (international units/kg) over time;
- To characterize the adverse events;
- To characterize the incidence of allergic reactions;
- To characterize subject compliance with prescribed regimens.

METHODS

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. A flow chart of the scheduled study events for the SE period of this study is provided in Table 1.

Subjects received a defined prophylaxis regimen of moroctocog alfa (AF-CC) for a minimum of 50 exposure days (EDs) over 6 months. Moroctocog alfa (AF-CC) was to be used exclusively for both prophylaxis and the treatment of any bleeds whether spontaneous or traumatic. Efficacy data was collected on the success of prophylaxis and detailed data was collected on the response of bleeds to therapy with moroctocog alfa (AF-CC). Safety data was collected on adverse events, especially the occurrence of FVIII inhibitors. The PK assessments made at Visits 2 and 3 for those subjects 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). A flow chart of the scheduled study events for the PK period of this study is provided in Table 2.

Table 1. Schedule of Events for Safety and Efficacy Period of Study

Study Period	**Screening**	**Crossover PK Period**		**Safety and Efficacy Period**							
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Final Contact**
Procedure	**Screening**[a]	**PK1**[b,c]	**PK2**[b,c]	**Month 0 Visit (Safety and Efficacy Day 1)**	**Month 1 Visit (Safety and Efficacy Month 1±1 Week)**	**Month 2 Visit (Safety and Efficacy Month 2±1 Week)**	**Month 3 Visit (Safety and Efficacy Month 3±1 Week)**	**Month 4 Visit (Safety and Efficacy Month 4±1 Week)**	**Month 5 Visit (Safety and Efficacy Month 5±1 Week)**	**Month 6 Visit (Safety and Efficacy Month 6±1 Week) and PK3**[b,d,e,f]	
Consent/assent	X										
Demographics	X										
Medical and drug history	X										
Vital signs	X			X	X		X			X	
Physical exam	X			X	X		X			X	
Height	X										
Weight	X			X	X		X			X	
HIV 1 & 2 antibodies	X										
CD4	X									X	
Hepatitis serology panel[g]	X										
Serum chemistry[h]	X									X	
Hematology[i]	X									X	
PT or INR	X										
Factor VIII:C[j]	X			X	X		X			X	
Factor VIII inhibitor[j]	X			X	X		X			X	
Enrollment and randomization[k]	X										
Dispense study drug				X	X	X	X	X	X		
Drug accountability					X	X	X	X	X	X	
Efficacy assessments					X	X	X	X	X	X	
Regimen adjustment					X	X	X	X	X		
Adverse event collection	X	X	X	X	X	X	X	X	X	X	X
Subject diary collection					X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
ELISA for Anti-FVIII[j], Anti-CHO[j]	X			X	X		X			X	

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Study Period	Screening	Crossover PK Period		Safety and Efficacy Period							
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Final Contact
Procedure	**Screening[a]**	**PK1[b,c]**	**PK2[b,c]**	**Month 0 Visit (Safety and Efficacy Day 1)**	**Month 1 Visit (Safety and Efficacy Month 1±1 Week)**	**Month 2 Visit (Safety and Efficacy Month 2±1 Week)**	**Month 3 Visit (Safety and Efficacy Month 3±1 Week)**	**Month 4 Visit (Safety and Efficacy Month 4±1 Week)**	**Month 5 Visit (Safety and Efficacy Month 5±1 Week)**	**Month 6 Visit (Safety and Efficacy Month 6±1 Week) and PK3[b,d,e,f]**	
ELISA Anti- TN8.2[j]	X									X	
Pharmacokinetic measurement on approximately 30 subjects[b]		X	X							X[f]	

ALT = alanine aminotransferase; AST = aspartate aminotransferase; Anti-CHO = Antibodies to Chinese hamster ovary cells; Anti-HAV = Antibodies to hepatitis A virus; Anti-HBc = Antibodies to hepatitis B core antigen; Anti-HBs = Antibodies to hepatitis B surface antigen; Anti-HCV = Antibodies to hepatitis C virus; CO2 = carbon dioxide; CHO = chinese hamster ovary cells (host cell line); CD4 = cluster of differentiation 4; ELISA = enzyme-linked immunosorbent assay; FVIII = Factor VIII; FVIII:C = Factor VIII activity in plasma; HIV = human immunodeficiency virus; INR = international normalized ratio; PK = pharmacokinetics; PT = prothrombin time; TN8.2 = The affinity ligand used during the moroctocog alfa (AF-CC) purification process.

a. The screening procedures took place only after consent/assent had been given. Therefore, they may have been performed on the day of consent or a specific screening day thereafter during the approximate 28-day screening period. The FVIII:C and FVIII inhibitor tests along with the ELISA antibody tests at Visit 1 were to be performed after a 72-hour washout of FVIII. If the study subject had administered FVIII within 72 hours of the Screening Visit, these tests may have been deferred to coincide with a planned 72-hour washout during the approximate 28-day screening period. The local and central laboratory test result from the Screening Visit, and not the study subject's historical FVIII activity levels, was required and documented in the subject source document for purposes of protocol inclusion.
b. The subjects completed their scheduled PK assessments before beginning the safety and efficacy period of the trial starting at Visit 4. All of the assessments applied to these PK subjects, as well as to the subjects who did not participate in the PK procedures. All subjects participated in the PK period of the trial were to have a final infusion of 50 IU/kg of moroctocog alfa (AF-CC) (PK3) after completion of the safety and efficacy period of the trial. This PK3 assessment occurred at Study Visit 11, and was ideally concurrent with Study Visit 10 for these subjects. There was also a wash out period of 72 hours prior to this PK3 assessment, as for the PK1 and PK2 assessments. The collection of PK3 blood samples, weight, and vital signs was identical to that described for PK1 or PK2.
c. Ideally, the crossover PK infusions (PK1 and PK2) occurred 1 week apart, but both occurred over the course of a maximum of 28 days. The first occurred no later than 28 days after consent the maximum duration of the screening period as soon as all eligibility criteria had been confirmed. Subjects used their regular FVIII replacement product in the intervals before and after collection of all PK samples for PK1 and PK2 and up to Visit 4. During PK1, subjects were instructed to return 1 week (5-9 days) after the dose administered during PK1, Day 1, and to complete a 3-day minimum washout prior to PK2, Day 1. During PK2, subjects were instructed to return for the Day 1 Visit of the safety and efficacy period of the trial (Visit 4), 1 week (5 to 9 days) following PK2, Day 1.
d. For subjects who terminated study participation early, the procedures of Study Visit 10 were performed as soon as practical to conclude the subject's participation. This served as an Early Termination Visit.
e. A final Safety Follow up contact occurred approximately 1 month after Study Visit 10 (or Visit 11 for PK subjects or Early Termination Visit if a subject withdraws). The

Table 1. Schedule of Events for Safety and Efficacy Period of Study

Study Period	Screening	Crossover PK Period		Safety and Efficacy Period							
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Final Contact
Procedure	Screening[a]	PK1[b,c]	PK2[b,c]	Month 0 Visit (Safety and Efficacy Day 1)	Month 1 Visit (Safety and Efficacy Month 1±1 Week)	Month 2 Visit (Safety and Efficacy Month 2±1 Week)	Month 3 Visit (Safety and Efficacy Month 3±1 Week)	Month 4 Visit (Safety and Efficacy Month 4±1 Week)	Month 5 Visit (Safety and Efficacy Month 5±1 Week)	Month 6 Visit (Safety and Efficacy Month 6±1 Week) and PK3[b,d,e,f]	

purpose of this contact was to collect safety information (Adverse Events and Concomitant Medications) that may have occurred during the approximately 4 weeks after a subject's final exposure to test article.

f. PK3 was termed Visit 11. This should be scheduled to coincide with Visit 10, the Month 6 Visit for safety and efficacy.
g. Hepatitis serology panel includes: Anti-HAV, Anti-HBc, Anti-HBs, HBsAg, Anti-HCV.
h. Serum chemistry includes: sodium, potassium, chloride, carbonate (or CO_2), ALT, AST, calcium, glucose, creatinine, urea, (total) bilirubin, phosphate, alkaline phosphatase, total protein, amylase, cholesterol and albumin.
i. Hematology included: Complete blood count, which includes hemoglobin, hematocrit, white blood cell count and differential, red blood cell and platelet count.
j. The screening labs and Visit 4, 5, 7 and 10 labs for FVIII:C and FVIII inhibitor, as well as ELISA tests for anti-FVIII/CHO/TN8.2 when measured occurred after a 72-hour washout.
k. Randomization and treatment on study occurred only after all screening eligibility criteria had been reviewed and documented in the subject source document. An external monitor confirmed subject eligibility following enrollment. Randomization occurred up to immediately before PK1 at Visit 2. For all study subjects, regardless of whether they were participating in the PK procedures of the trial, the Investigator/study site staff consulted with the clinical trial manager no less than 3 business days prior to a planned Visit 4 to allow for shipping of the test article to the study site.

Table 2. Schedule of Events for PK1, PK2, and PK3 Assessments Occurring at Visits 2, 3, and 11, Respectively

	PK Day 1									PK Day 2			PK Day 3
Procedure		**Predose -2-0 hr**	**Infusion 0-2 min**	**15 min (±2 min)**	**30 min (±3 min)**	**1 hr (±6 min)**	**3 hr (±18 min)**	**6 hr (±30 min)**	**9 hr (±60 min)**	**24 hr (±60 min)**	**28 hr (±60 min)**	**32 hr (±60 min)**	**48 hr (±120 min)**
Vital signs	3 day washout	X								X			X
Weight		X											
Test article administration			X										
CBC		X											
FVIII:C		X		X	X	X	X	X	X	X	X	X	X
FVIII Inhibitor (BIA)		X											

Post-infusion samples were collected within the time variances relative to the time of initiating the FVIII test article injection as indicated in the Table above. The schedule of events is identical for all three PK assessments.

Samples for FVIII:C and FVIII inhibitor were collected at the site but analyzed at the central laboratory.

Central laboratory confirmation of PK eligibility (screening FVIII:C ≤1% and FVIII inhibitor negative) was required before administration of test article on PK1, Day 1, Study Visit 2. Subjects must not had infused FVIII or FVIII containing products for a minimum of 72 hours before receiving the PK infusion of 50 IU/kg at Study Visit 2, 3 and 11. The Study Visit 11 (PK3) assessment should had occurred at the same time as Study Visit 10 (Month 6 Safety and Efficacy Visit). The first day of PK3 might had occurred in conjunction with general activities that all subjects must had for the safety and efficacy evaluation that occurred at the Month 6 Visit. Subjects could not infuse any FVIII containing products after each infusion until all samples had been collected. If a bleed occurred that compromised the PK assessment (or delayed a PK assessment), the subject treated his bleed and repeated (or rescheduled) the PK Visit after his bleed had resolved. If a second bleed occurred, necessitating repeat of delay of the PK, the subject was removed from the PK period of the study and entered into the safety and efficacy period of the study. Ideally, PK1 and PK2 infusions occurred 1 week apart, but must had occurred over the course of a maximum of 28 days. They were scheduled to begin as soon as all eligibility criteria had been confirmed, following subject enrollment and randomization. Subjects used their regular FVIII replacement product in the intervals before and after collection of PK1 and PK2 samples and up to Visit 4. The safety and efficacy period of the trial commenced soon (5-9 days) after the completion of the final blood draw following PK2. Only study drug should have been infused once the subject started the safety and efficacy period of the trial. All subjects participating in the PK period of the trial had a final infusion of 50 IU/kg of moroctocog alfa (AFCC) after completion of the safety and efficacy period of the trial (6-month PK assessment, PK3).

AF-CC = albumin-free cell culture; BIA = Bethesda Inhibitor Assay; CBC = complete blood count; FVIII = Factor VIII; FVIII:C = Factor VIII activity in plasma; PK = pharmacokinetics.

Number of Subjects (Planned and Analyzed): A total of 100 subjects were planned to enroll for safety and efficacy evaluation and 30 subjects were evaluated for PK evaluation. A total of 94 subjects were enrolled and treated (26 in the United States, 13 in Hungary; 5 in Sweden, 2 in Finland and Germany, 29 in Poland; 10 in New Zealand; 5 in Australia, and 1 each in Italy and Belgium).

Diagnosis and Main Criteria for Inclusion: Male subjects ≥12 years of age with severe or moderately severe hemophilia A (FVIII activity ≤2%), previously treated with 150 EDs to any FVIII product, negative past medical history of a FVIII inhibitor were included. Subjects were excluded on the basis of history of a FVIII inhibitor, presence of a bleeding disorder in addition to hemophilia, known hypersensitivity to hamster protein. To be eligible for the PK period of the trial, subjects were required to have a FVIII activity ≤1%.

Study Treatment: Prophylaxis was initiated with a dose of 30±5 IU/kg 3 times per week. For the crossover PK period of the study, subjects received 50 IU/kg single dose infusions of moroctocog alfa (AF-CC) and FLrFVIII, 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 subjects 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.

Efficacy and Safety Endpoints:

Primary Endpoint:

- The primary safety endpoint of this study was the incidence of de novo FVIII inhibitors associated with the use of moroctocog alfa (AF-CC) in the study subject population. The primary efficacy endpoint of this study was to establish the bioequivalence of moroctocog alfa (AF-CC) and a FLrFVIII using the OS FVIII assay.

Secondary Endpoints:

- To characterize the PK of moroctocog alfa (AF-CC) in comparison to FLrFVIII and over time;
- To characterize the efficacy of moroctocog alfa (AF-CC) in preventing and treating bleeding episodes during prophylaxis treatment;
- To characterize the efficacy response of both prophylactic and on-demand infusions of moroctocog alfa (AF-CC);
- To characterize the rate of "Less than Expected Therapeutic Effect" (LETE) responses of moroctocog alfa (AF-CC) when used either prophylactically or for treatment of a bleeding episode ("on-demand") or in the instance of low recovery;

- To characterize the consumption of moroctocog alfa (AF-CC) (international units/kg) over time;
- To characterize the adverse events;
- To characterize the incidence of allergic reactions;
- To characterize subject compliance with prescribed regimens.

Safety Evaluations: Safety was monitored from the time subjects signed the informed consent and was evaluated until the time of the final study contact. All 94 subjects treated with at least 1 dose of moroctocog alfa (AF-CC), comprising the intent-to-treat (ITT) subject population, were included in the safety analysis. Exposure and safety data were also examined for the subsets of subjects aged ≤16 years and those >16 years.

Statistical Methods:

Analysis Set:

Per-Protocol (PP) Population: It included all subjects who were deemed to be eligible, with no protocol violations, who completed PK1 (Visit 2) and PK2 (Visit 3) for bioequivalence testing of moroctocog alfa (AF-CC) and FLrFVIII, and who had adequate washout periods preceding the PK assessments. A ≥72-hour washout of FVIII was required before all PK infusions. PK analyses were performed on the PP population.

Intent-to-Treat Population: It included all enrolled (randomized) subjects who received at least 1 dose of study drug (either moroctocog alfa [AF-CC] or FLrFVIII). All safety analyses (other than the primary safety objective of FVIII inhibitor development rate) were performed on the ITT population.

Modified Intent-to-Treat (mITT) Population: It included the subset of ITT subjects who received at least 1 dose of moroctocog alfa (AF-CC). The mITT population was used to support the primary safety objective of assessing the FVIII inhibitor development rate and the secondary efficacy objectives.

In general, all efficacy and safety endpoints were summarized with descriptive statistics as appropriate. Descriptive statistics were used to summarize demographic and baseline data on the study population, as well as data on hemostatic efficacy, treatment-emergent adverse events (TEAEs) and treatment-emergent hemophilia events, LETE, and annualized bleeding episodes. For continuous variables, number, mean, standard deviation, median, minimum, and maximum are provided. Interquartile ranges and 95% confidence intervals were provided where meaningful. For categorical variables, frequency and percentage are presented for each category.

RESULTS

Subject Disposition and Demography: Ninety-four (94) subjects enrolled and were treated with at least 1 dose of moroctocog alfa (AF-CC) in the study and were included in the ITT population. Subject disposition is summarized in Table 3.

Table 3. Summary of Subject Disposition

Characteristic	Subjects (N=94)
Subjects treated	94
PK period	31
SE period	94
PK over time (PK3)	27
Reason for conclusion of subject participation	
Completed PK period (PK1 and PK2)	31
Completed SE period and final study procedures	90 (96%)[a]
Accrued ≥50 EDs during the SE period (evaluable population)	89
Discontinued treatment	4 (4%)[a]
Adverse event	0
Adverse event - development of inhibitor	1 (1%)[a]
Investigator request	2 (2%)[a]
Other	1 (1%)[a]
Days on study[b]	
Number of subjects	94
Mean	239.4
SD	23
Median	240.5
Min, Max	149, 301
Days on RP treatment[c]	
Number of subjects	94
Mean	172.0
SD	26
Median	178.0
Min, Max	1, 213

ED = exposure day; Max = maximum; Min = minimum; N = number of subjects; PK = pharmacokinetic; RP = routine prophylaxis; SE = safety and efficacy; SD = standard deviation.

a. Number of subjects who received at least 1 infusion of study drug (moroctocog alfa [AF-CC]) was used for the denominators.

b. Days on Study = (Date of last contact) - (Date informed consent signed) +1

c. Days on routine prophylaxis treatment = (Date of last visit) - (Date of first RP dose of study drug) +1

Four (4) subjects discontinued treatment early, before completing 6 months of routine prophylaxis treatment during the SE period of the trial.

Demographic and baseline characteristics are summarized on Table 4. All subjects (100%) enrolled in the study were male.

Table 4. Summary of Demographics and Baseline Characteristics

Characteristics	Data (N=94)
Age (years)	
N	94
Mean	27.7
SD	12.8
Median	24
Min, Max	12, 60
Age category, n (%)	
12-16 years	18 (19.1%)
17-65 years	76 (80.9%)
Sex, n (%)	
Male	94 (100.0%)
Race, n (%)	
Asian	1 (1.1%)
Other: Arab	1 (1.1%)
Other: Fijian Indian	1 (1.1%)
Other: Mid Eastern Iranian	1 (1.1%)
Other: Mixed race	1 (1.1%)
White	89 (94.7%)
Ethnic origin, n (%)	
Hispanic or Latino	4 (4.3%)
Non-hispanic and Non-latino	90 (95.7%)
Weight (kg)	
N	94
Mean	72.7
SD	16.1
Median	73.1
Min, Max	42.0, 120.3
Height (cm)	
N	93
Mean	176.2
SD	7.7
Median	176.0
Min, Max	156.0, 193.0

Max = maximum; Min = minimum; N = number of subjects; SD =standard deviation.

Baseline Disease Characteristics: Hemophilia history is summarized in Table 5. All 94 subjects had ≥150 previous EDs to FVIII replacement products. Of the 94 subjects in the SE period of the trial, 74 (79%) subjects had at least 1 target joint identified (a target joint was defined as a major joint into which repeated bleeding occurred with clinical signs and/or symptoms of underlying target joint damage).

Table 5. Summary of Hemophilia A History

Variables	Statistics	SE Period (N=94)
HIV status	Positive	9 (9.6%)
	Negative	84 (89.4%)
	Missing	1 (1.1%)
HCV status	Positive	66 (70.2%)
	Negative	27 (28.7%)
	Missing	1 (1.1%)
Previous exposure days	≥150 days	94 (100 %)
Hemophilia severity[a]	≤1%	86 (91.5%)
	>1%, ≤2%	7 (7.4%)
	>2%, ≤5%	1 (1.1%)
Presence of target joints	No	20 (21.3%)
	Yes	74 (78.7%)

FVIII = Factor VIII; HCV = hepatitis C virus; HIV = human immunodeficiency virus; N = number of subjects; SE = safety and efficacy.
a. Central lab FVIII activity level results at Screening.

Efficacy and Pharmacokinetic Results:

Bioequivalence of Moroctocog Alfa (Albumin Free-Cell Culture) and Full-Length Recombinant Factor VIII (Pharmacokinetic 1 and Pharmacokinetic 2): A summary of the descriptive statistics of plasma FVIII:C PK parameters for the 30 subjects evaluable for bioequivalence testing and the results from the statistical analysis for these parameters is presented in Table 6.

Table 6. Pharmacokinetic Parameter Estimates for Moroctocog Alfa (AF-CC) and Full-Length Recombinant Factor VIII in Previously Treated Subjects With Hemophilia A (Based on Central Laboratory Potency Assessment)

Treatment	C_{max} (IU/mL)	AUC_t (IU·h/mL)	AUC_{inf} (IU·hr/mL)	$t_{½}$ (hr)	K-value (IU/dL per IU/kg)	In vivo Recovery (%)
Full-Length Recombinant Factor VIII						
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%	-

AF-CC = albumin-free cell culture; AUC_{inf} = area under the plasma concentration-time curve from time zero to infinity; AUC_t = area under the plasma concentration-time curve from zero to the last measurable concentration; CI = confidence interval; C_{max} = peak concentration; IU = international unit; K = incremental recovery; LS = least squares; Max = maximum; Min = minimum; SD=standard deviation; $t_{1/2}$ = terminal-phase elimination half-life.
a. The 90% CI about the ratio of the moroctocog alfa (AF-CC)-to-full length recombinant factor VIII means were obtained using the average bioequivalence procedure for a 2 × 2 crossover design provided in WinNonlin Professional version 4.1

Moroctocog Alfa (Albumin Free-Cell Culture) PK Results at Baseline Versus Month 6 (Pharmacokinetic 3): A summary of the descriptive statistics of FVIII:C PK parameters for the 25 evaluable subjects and the results from the statistical analysis are presented in Table 7.

Table 7. Pharmacokinetic Parameter Estimates for Moroctocog Alfa (AF-CC) At Baseline and Month 6 in Previously Treated Subjects With Hemophilia A (Based on Central Laboratory Potency Assessment)

Visit	C_{max} (IU/mL)	AUC_t (IU·hr/mL)	AUC_{inf} (IU·hr/mL)	$t_{½}$ (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%	-

AF-CC = albumin-free cell culture; AUC_{inf} = area under the plasma concentration-time curve from time zero o infinity; AUC_t = area under the plasma concentration-time curve from zero to the last measurable concentration; CI = confidence interval; C_{max} = peak concentration; FVIII:C = Factor VIII activity in plasma. hr = hour; IU = international unit; K = incremental recovery; LS = least squares; Max = Maximum; Min = Minimum; PK = pharmacokinetic; SD = standard deviation; $t_{½}$ = terminal-phase elimination half-life.

a. The higher mean and SD was attributed to change in PK profile from Baseline PK to Month 6 PK for 1 subject ($t_{½}$ = 12.7 hr at Baseline and 75.7 hr at Month 6). Excluding this subject from the Month 6 analysis, the mean (±SD) $t_{½}$ value was 11.8 ± 6.2 hr at Month 6 (n=24).

b. The 90% CI about the ratio of the Month 6 to baseline means were obtained using the two 1-sided tests procedure for log-transformed data using WinNonlin Professional version 4.1.

Exposure to Moroctocog Alfa (Albumin Free-Cell Culture): A summary of dosing and EDs to morocotcog alfa (AF-CC) based on manufacturer's labeled potency for all 94 subjects in the ITT population is presented in Table 8.

All 94 subjects received moroctocog alfa (AF-CC) for routine prophylaxis and, in some cases, for intermittent prophylaxis to supplement that routine prophylaxis. As noted in Table 8, a cumulative total of 14,368,065 IU of moroctocog alfa (AF-CC) was administered during all prophylactic infusions, excluding data subsequent to date of inhibitor development for 1 subject. All subjects began routine prophylaxis treatment at a dose of 30 IU/kg 3 times a week. Only 7 dose escalations were prescribed for 6 subjects during the course of the study.

Table 8. Summary of Moroctocog Alfa (AF-CC) Consumption for Efficacy Evaluation

Variable	Statistics	Primary Reason for Infusion			
		Prophylaxis[a]	On Demand/ Follow-up Treatment	PK[b]	Total
Total units (IU) per subject	Cumulative total	14368065	658004	231749	15257818
	N(of subject)	93	53	31	93
	Mean	154495.3	12415.2	7475.8	164062.6
	SD	43410.1	17012.6	2195.1	45493.8
	Median	153810	6170	7808	165435
	Interquartile range	128436, 182701	3123, 14612	5986, 8943	142326, 192805
	Min, Max	25090, 284934	530, 97854	2863, 11563	25090, 299546
Range of infusion (IU)	Min, Max	530, 5205	530, 6246	2600, 5837	530, 6246
Dose (IU/kg) per infusion	N(of infusions)	6401	280	58	6739
	Mean	30.7	33.7	50.3	31.0
	SD	4.2	11.6	1.0	5.1
	Median	30.2	30.6	50.0	30.2
	Interquartile range	27.9, 32.6	28.0, 34.7	49.6, 50.9	28.0, 32.8
	Min, Max	6.8, 76.9	6.4, 74.4	48.6, 52.4	6.4, 76.9
Number of infusions per subject	Cumulative Total	6406	282	59	6747
	N(of subject)	94	53	32	94
	Mean	68.1	5.3	1.8	71.8
	SD	14.2	5.8	0.4	14.2
	Median	72	3	2	76
	Interquartile range	65, 77	1, 7	2, 2	69, 79
	Min, Max	1, 85	1, 26	1, 2	1, 93
Exposure days per subject	Cumulative Total	6403	265	59	6713
	N(of subject)	94	53	32	94
	Mean	68.1	5.0	1.8	71.4
	SD	14.2	5.5	0.4	14.1
	Median	72	3	2	76
	Interquartile range	65, 77	1, 7	2, 2	68, 79
	Min, Max	1, 85	1, 26	1, 2	1, 92

Recorded infusions without associated dose information were not included in summary statistics for some parameters, including total units per subject, range of infusion and dose per infusion. One (1) subject was completely excluded from these statistics due to unknown dosing information for his only confirmed infusion.
Excluded data from date of inhibitor development for 1 subject.
AF-CC = albumin-free cell culture; FVIII = factor VIII; IU = international units; Max = maximum; Min = minimum; PK = pharmacokinetic; Std. Dev.=standard deviation
a. Included routine prophylaxis and intermittent prophylaxis.
b. Excluded infusions with full-length recombinant FVIII.

Annualized Bleeding Rates in Prophylaxis Subjects: Fifty-seven (57; 60.6%) subjects reported no spontaneous bleeding while on routine prophylaxis with moroctocog alfa (AF-CC) and 43 subjects (45.7%) had no bleeding episodes of any type. Bleeding episodes that required treatment with FVIII and that occurred while the subject was on routine prophylaxis were considered in the calculation of the annualized bleeding rate. In total, 180 such bleeding episodes (all treated with moroctocog alfa [AF-CC]), including

88 spontaneous and 92 traumatic bleeds, were reported during routine prophylaxis (Table 9).

Table 9. Summary of Annualized Bleed Rates During Routine Prophylaxis

Statistic	ABR[a] for Each Type of Bleed (Number of Bleeds)		
	Spontaneous (N=88)	Traumatic (N=92)	Total (N=180)
Mean	1.9	2.0	3.9
SD	4.1	4.1	6.5
Median	0.0	0.0	1.9
Minimum	0.0	0.0	0.0
Maximum	30.1	23.3	42.1
95% CI	(1.1, 2.7)	(1.2, 2.8)	(2.6, 5.2)

Number of subjects analyzed = 94; cumulative time on routine prophylaxis treatment = 2350 weeks.
ARB = annualized bleeding rates; CI = confidence interval; SD = standard deviation; N = number of subjects.
a. Annualized bleed rate calculate for each subject, then summarized.

Time From Previous Moroctocog Alfa (Albumin Free-Cell Culture) Infusion to New Bleed During Prophylaxis: During routine prophylaxis with moroctocog alfa (AF-CC), 187 bleeds occurred (Table 10). Of these bleeds, 61.1% (110 of 180 bleeds) occurred ≤48 hours after the last dose of moroctocog alfa (AF-CC) and 38.9% (70 of 180 bleeds) occurred >48 hours after the last dose of moroctocog alfa (AF-CC).

Table 10. Number of Spontaneous and Other Types of Bleeding Episodes by Time Between Previous Prophylaxis Infusion and Start of Bleed (N=94)

Time between last prophylaxis infusion and start of bleed										Total Bleeding Episodes
≤24 hours		>24-≤48 hours		>48-≤72 hours		>72 hours		Unknown[a]		
Spon bld	Other	Spon bld	Other	Spon bld	Other	Spon bld	Other	Spon bld	Other	
13	20	33	44	24	12	18	16	3	4	187

N = number of subjects; Spon bld = spontaneous new bleed.
a. Bleeds with unknown start time or bleeds in which previous prophylaxis dose was before the start of the safety and efficacy period of the study.

Less Than Expected Therapeutic Effect in the in the Prophylaxis Setting: In total, 25 spontaneous bleeds during routine prophylaxis in 13 subjects met the predefined criteria to be considered LETE. The incidence rate of LETE during prophylaxis was 0.4% (25 events of LETE/6347 routine prophylactic infusions). Multiple events of LETE were identified for 3 subjects, including 1 subject (7 LETE events), 1 subject (6 LETE events) and 1 subject (2 LETE events). All other subjects for whom LETE was reported had 1 event of LETE.

On Demand Treatment:

Moroctocog Alfa (Albumin Free-Cell Culture) Dosing Summary for On-Demand Treatment: Fifty-three (53) subjects received moroctocog alfa (AF-CC) for on-demand treatment (Table 8) during the study (including subjects who reported on-demand use before beginning their routine prophylaxis). The cumulative moroctocog alfa (AF-CC) dose for on-demand treatment was 658,004 IU. The cumulative number of EDs for on-demand treatment was 265. A total of 282 on-demand infusions of moroctocog alfa (AF-CC) were administered with a median dose per infusion of 30.6 IU per subject (range, 6.4 to 74.4 IU). The median

number of on-demand infusions per subject was 3 (range, 1 to 26 infusions). The median and mean doses for on-demand treatment were 30.6 and 33.7 IU/kg, respectively, and these were similar to the median and mean dose reported during prophylaxis treatment (30.2 and 30.7 IU/kg, respectively), suggesting that subjects tended to treat bleeds with an on-demand dose similar to their regularly scheduled prophylaxis dose.

Location of Bleeds: In total, 187 bleeds were treated with on-demand infusions of moroctocog alfa (AF-CC) during the study. Bleeds most frequently occurred in joints (114 of 187 bleeds; 61%). Bleeds also frequently occurred in soft tissue/muscle (43 of 187 bleeds; 23%).

Treatment Response Measured Using a 4-Point Scale: The response to on-demand treatment with moroctocog alfa (AF-CC) was assessed using a 4-point scale. Of the 187 initial infusions to treat a bleed, the response to 132 (70.6%) infusions was rated as either excellent or good, including 44 (23.5%) initial infusions rated "excellent" and 88 (47.1%) initial infusions rated "good." Forty-five (45) of 187 initial infusions (24.1%) to treat bleeds were rated "moderate." Five (5) of 187 initial infusions (2.7%) were rated "no response," and 5 of 187 initial infusions (2.7%) were not assessed, including 1 that used commercial FVIII. The distribution of ratings was similar regardless of location of bleed, suggesting moroctocog alfa (AF-CC) was equally efficacious at different locations.

Less Than Expected Therapeutic Effect in the On-Demand Setting: LETE in the on-demand setting was defined as 2 successive "no response" ratings on the efficacy scale, for consecutive infusions to treat the same bleed by the subject, in the absence of confounding factors. Two (2) consecutive "no response" ratings were noted for 2 subjects. This was considered LETE for 1 subject. The incidence of LETE in the on-demand setting was 0.5% (1 event of LETE in 1 subject /187 bleeding episodes treated with on-demand infusions across subjects).

Treatment Response to First Moroctocog Alfa (Albumin Free-Cell Culture) Infusion by Location of Bleed: A summary of response ratings to the first infusion of moroctocog alfa (AF-CC) for bleeds by location is presented in Table 11.

Table 11. Summary of Response to First Infusion to Treat Bleeding Episode by Bleed Location

Response to First Infusion	Bleed Location				Total Number of Bleeds
	Joint	Soft Tissue/Muscle	Other Site	Multiple Sites	
Excellent	25 (21.9)	13 (30.2)	2 (16.7)	4 (22.2)	44
Good	61 (53.5)	14 (32.6)	6 (50.0)	7 (38.9)	88
Moderate	24 (21.1)	11 (25.6)	4 (33.3)	6 (33.3)	45
No Response	3 (2.6)	1 (2.3)	0 (0.0)	1 (5.6)	5
Not Assessed	1 (0.9)	4 (9.3)	0 (0.0)	0 (0.0)	5[a]
Total	114	43	12	18	187

a. Included 1 infusion with commercial FVIII that occurred before routine prophylaxis began.

Treatment Response to First Moroctocog Alfa (Albumin Free-Cell Culture) Infusion by Number of Infusions: A summary of response to the first infusion of moroctocog alfa

(AF-CC) by the number of infusions needed to treat a bleeding episode is presented in Table 12.

Table 12. Summary of Response to First Infusion to Treat Bleeding Episode by Number of Infusions Needed for Resolution

Response to First Infusion	Number of Subjects	Number of Infusions					Total Number of Bleeds
		1	2	3	4	>4	
Excellent	28	42 (95.5)	2 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	44
Good	28	69 (78.4)	16 (18.2)	3 (3.4)	0 (0.0)	0 (0.0)	88
Moderate	19	24 (53.3)	16 (35.6)	2 (4.4)	0 (0.0)	3 (6.7)	45
No Response	5	0 (0.0)	0 (0.0)	2 (40.0)	2 (40.0)	1 (20.0)	5
Not Assessed	3	4 (80.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	5[a]
Total	53	139 (74.3)	34 (18.2)	7 (3.7)	3 (1.6)	4 (2.1)	187

a. Included 1 infusion with commercial FVIII that occurred before routine prophylaxis began.

Moroctocog Alfa (Albumin Free-Cell Culture) Consumption Over Time: Table 13 presents moroctocog alfa (AF-CC) consumption based on monthly and yearly estimates of usage in the study population. Mean annual per subject routine prophylactic usage of moroctocog alfa (AF-CC) was 4337.3 IU/kg per year, in contrast to annualized intermittent prophylaxis and on-demand use of 268.9 and 362.5 IU/kg per subject, respectively.

Table 13. Summary of Moroctocog Alfa (AF-CC) Consumption Per Month and Per Year

Variable[a]	Statistics	Primary Reason for Infusion			
		Intermittent Prophylaxis	Routine Prophylaxis	On Demand/ Follow-up Treatment	Total
Total dose (IU/kg) per 30-days	N	17	93	53	93
	Mean	22.1	356.2	29.8	377.2
	SD	38.3	69.2	41.3	70.7
	Median	10	357	16	378
	Inter-quartile	5, 17	331, 397	7, 37	345, 410
	Min, Max	2, 165	82, 582	1, 215	149, 632
Number of infusions per 30-days	N	17	94	53	94
	Mean	0.6	11.5	0.9	12.1
	SD	0.7	2.2	0.9	2.1
	Median	0	12	1	13
	Inter-quartile	0, 1	11, 13	0, 1	12, 13
	Min, Max	0, 3	0, 15	0, 4	0, 15
Total dose (IU/kg) per year	N	17	93	53	93
	Mean	268.9	4337.3	362.5	4593.0
	SD	466.1	842.2	502.2	860.5
	Median	116	4352	200	4602
	Inter-quartile	66, 204	4034, 4830	82, 447	4204, 4988
	Min, Max	30, 2012	1000, 7092	13, 2613	1815, 7696
Number of infusions per year	N	17	94	53	94
	Mean	6.7	140.5	10.9	147.8
	SD	8.2	26.9	11.4	25.2
	Median	4	149	7	155
	Inter-quartile	2, 7	140, 155	2, 14	149, 157
	Min, Max	2, 36	3, 179	2, 52	3, 186

Recorded infusions without associated dose information are not included in summary statistics for some parameters, including total units per subject, range of infusion and dose per infusion. One is completely excluded from these statistics due to unknown dosing information for his only confirmed infusion.
AF-CC = albumin-free cell culture; Min = minimum; Max = maximum; N = number of subject; SD = standard deviation.
a. Total dose and number of infusions were normalized over a 30-day month or over a year for each subject and then summarized.

Safety Results:

Exposure and safety data were examined for subsets of subjects aged ≤16 years and those >16 years.

Development of Inhibitor: Transient low-titer inhibitors were detected in 2 of 94 subjects (2.1% of the study population) in this study. Both inhibitors were detected in clinically asymptomatic subjects during routine protocol-specified surveillance tests. Bayesian methodology was employed in this study to calculate the probability that the population (true) inhibitor rate for the test article is below a pre-defined acceptable value. The posterior distribution of the inhibitor rate in this study, given the data generated, is a beta distribution with parameters $\alpha+x$ and $\beta+n-x$, where x is the number of observed inhibitors, n is the number of subjects analyzed (and α and β are 2.5 and 110, respectively). From this distribution, the probability that the product inhibitor rate is below the threshold of 4.4% and

the product's maximum intrinsic (true) inhibitor rate, calculated with 95% probability, are presented in Table 14.

Table 14. Bayesian Posterior Distribution of Inhibitor Rate

				Posterior Beta Distribution Characteristics			
FVIII Inhibitor Nijmegen Result (BU/mL)	**Number of Inhibitors**	**Number of Subjects Analyzed**	**Observed Inhibitor Rate (%)**	**Alpha[a]**	**Beta[b]**	**Posterior Probability[c]**	**95% Upper Limit of Inhibitor Rate (%)[d]**
≥0.6	2	94	2.13%	4.5	202	0.9666	4.07%

a. Prior alpha of 2.5 plus the number of observed inhibitors.
b. Prior beta of 110 plus the number of subjects analyzed minus the number of observed inhibitors.
c. Posterior probability was the probability that the true inhibitor rate was less than the upper acceptable limit of 4.4%. A posterior probability >0.95 was deemed acceptable.
d. The 95% upper limit of the true inhibitor rate (the maximum rate calculated with at least 95% probability) based on the posterior distribution. An inhibitor rate <4.4% was deemed acceptable.

Most Frequent Treatment-Emergent Adverse Events: Fifty-eight (58) of 94 (61.7%) subjects reported at least 1 TEAE during the study. The most frequent TEAEs (reported in ≥5% of subjects) affected the body as a whole (headache [24.5%], infection [18.1%], accidental injury [9.6%], pain [6.4%], and fever [5.3%]), the cardiovascular system (hypertension [5.3%]), the digestive system (nausea [6.4%] and diarrhea [5.3%]), and the respiratory system (pharyngitis [13.8%] and rhinitis [6.4%]). A summary of all TEAEs reported regardless of causality or toxicity grade is presented in Table 15.

Table 15. Summary of Treatment Emergent Adverse Events (Excluding Hemophilia Events) by Body System and COSTART Term

Body System Event	Number (%) of Subjects N=94
Any event[a]	58 (61.7)
Body as a whole	
Headache	23 (24.5)
Infection	17 (18.1)
Accidental injury	9 (9.6)
Pain	6 (6.4)
Fever	5 (5.3)
Asthenia	4 (4.3)
Back pain	4 (4.3)
Flu syndrome	4 (4.3)
Allergic reaction	3 (3.2)
Neoplasm	2 (2.1)
Cellulitis	1 (1.1)
Hangover effect	1 (1.1)
Injection site inflammation	1 (1.1)
Injection site pain	1 (1.1)
Injection site reaction	1 (1.1)
Neck pain	1 (1.1)
Cardiovascular system	
Hypertension	5 (5.3)
Hemorrhage	1 (1.1)
Migraine	1 (1.1)
Digestive system	
Nausea	6 (6.4)
Diarrhea	5 (5.3)
Vomiting	3 (3.2)
Tooth disorder	2 (2.1)
Biliary pain	1 (1.1)
Dyspepsia	1 (1.1)
Gastroenteritis	1 (1.1)
Gastroesophageal reflux disease	1 (1.1)
Gingivitis	1 (1.1)
Liver function tests abnormal	1 (1.1)
Rectal hemorrhage	1 (1.1)
Hemic and lymphatic system	
Anemia	1 (1.1)
Iron deficiency anemia	1 (1.1)
Lymphadenopathy	1 (1.1)
Metabolic and nutritional	
Weight gain	1 (1.1)
Musculoskeletal system	
Arthralgia	3 (3.2)
Joint disorder	2 (2.1)
Arthritis	1 (1.1)
Musculoskeletal stiffness	1 (1.1)
Myalgia	1 (1.1)
Tenosynovitis	1 (1.1)

Table 15. Summary of Treatment Emergent Adverse Events (Excluding Hemophilia Events) by Body System and COSTART Term

Body System Event	Number (%) of Subjects N=94
Nervous system	
Paresthesia	3 (3.2)
Depression	1 (1.1)
Sleep disorder	1 (1.1)
Vertigo	1 (1.1)
Respiratory system	
Pharyngitis	13 (13.8)
Rhinitis	6 (6.4)
Upper respiratory infection	4 (4.3)
Cough increased	3 (3.2)
Bronchitis	1 (1.1)
Wheezing	1 (1.1)
Skin and appendages	
Erythema	1 (1.1)
Furunculosis	1 (1.1)
Pruritic rash	1 (1.1)
Rash	1 (1.1)
Skin disorder	1 (1.1)
Urticaria	1 (1.1)
Special senses	
Ear pain	2 (2.1)
Conjunctivitis	1 (1.1)
Urogenital system	
Cystitis	1 (1.1)
Terms not classifiable	
Reaction unevaluable	1 (1.1)
Adverse event associated with miscellaneous factors	
Local reaction to procedure	2 (2.1)

AEs and SAEs are not separated out.
AEs = adverse events; COSTART = Coding Symbols for Thesaurus of Adverse Reaction Terms; N = number of subjects; SAEs = serious adverse events.
a. Any adverse event total is not necessarily the sum of the individual events since a subject may have reported 2 or more different events.

Most Frequent Treatment-Emergent Hemophilia Events: Thirty-one (31) subjects (33%) reported at least 1 treatment-emergent hemophilia event. The most frequent (reported in ≥5% of subjects) treatment-emergent hemophilia events affected the body as a whole (pain [10.6%]) and the musculoskeletal system (arthralgia [17%] and joint disorder [8.5%]). All treatment-emergent hemophilia events reported, regardless of causality or toxicity grade, are presented in Table 16.

Table 16. Summary of Treatment Emergent Hemophilia Events by Body System and COSTART Term

Body System Event	Number (%) of Subjects N=94
Any Event[a]	31 (33.0)
Body as a whole	
Pain	10 (10.6)
Accidental injury	2 (2.1)
Back pain	2 (2.1)
Asthenia	1 (1.1)
Traumatic hematoma	1 (1.1)
Cardiovascular system	
Vasodilatation	1 (1.1)
Digestive system	
Tooth disorder	1 (1.1)
Hemic and lymphatic system	
Ecchymosis	2 (2.1)
Factor VIII inhibition	2 (2.1)
Metabolic and nutritional	
Peripheral edema	1 (1.1)
Musculoskeletal system	
Arthralgia	16 (17.0)
Joint disorder	8 (8.5)
Arthritis	2 (2.1)
Muscle hemorrhage	1 (1.1)
Musculoskeletal stiffness	1 (1.1)
Skin and appendages	
Erythema	1 (1.1)

AEs and SAEs are not separated out.
AEs = adverse events; COSTART = Coding Symbols for Thesaurus of Adverse Reaction Terms; N = number of subjects; SAEs = serious adverse events.
a. Any adverse event total is not necessarily the sum of the individual events since a subject may have reported 2 or more different events.

Related Treatment Emergent Adverse Events and Hemophilia Events: All TEAEs and treatment-emergent hemophilia events considered by Investigators to be at least possibly related to moroctocog alfa (AF-CC) are summarized in Table 17.

Table 17. Summary of Related Treatment Emergent Adverse Events and Hemophilia Events by Body System and COSTART Term

Body System Event	All Subjects N=94
Any eventa	3 (3.2)
Body as a whole	
Asthenia	1 (1.1)
Cardiovascular system	
Hemorrhage	1 (1.1)
Hemic and lymphatic system	
Factor VIII inhibition	2 (2.1)
Musculoskeletal system	
Arthralgia	1 (1.1)

AEs and SAEs are not separated out.
AEs = adverse events; COSTART = Coding Symbols for Thesaurus of Adverse Reaction Terms; N = number of subjects; SAEs = serious adverse events.
a. Any adverse event total is not necessarily the sum of the individual events since a subject may have reported 2 or more different events.

Serious Adverse Events and Serious Hemophilia Events: Two (2) treatment-emergent serious adverse events (SAEs) were reported. One (1) subject reported an accidental injury (right maxillary sinus fracture), and 1 subject reported cellulitis of the knee. Both events were considered definitely not related to moroctocog alfa (AF-CC) and resolved.

Both cases of FVIII inhibitor that developed were reported as serious hemophilia events; both events were considered related to moroctocog alfa (AF-CC). No other serious hemophilia events were reported in this trial.

Thus, in total, 2 SAEs (accidental injury and cellulitis) and 2 serious hemophilia events of FVIII inhibitor were reported by 4 subjects (1 event each).

Discontinuations due to Adverse Events: One (1) subject was withdrawn after detection of a transient, clinically silent inhibitor. No other subject was discontinued for reasons related to safety. One (1) subject also developed a transient, clinically silent inhibitor that was detected at his final study visit (Visit 10) and thus he was not withdrawn from the study.

Deaths: There were no deaths reported during the study.

Laboratory Evaluations: Treatment-emergent anemia (hemoglobin of 126.0 g/L) was reported for 1 subject; this was deemed unrelated to study drug. No other individual subject presented any laboratory changes of clinical importance. There were no clinically important abnormalities related to moroctocog alfa (AF-CC) for blood chemistry or hematology changes during the study.
Hypertension was reported as a TEAE for 5 (5.3%) subjects. All 5 TEAEs were either mild (n=4) or moderate (n=1) in severity and deemed unrelated to test article with respect to vital signs and body weight. Otherwise, no clinically important changes from baseline were observed concerning vital signs or body weight.

CONCLUSION:

- Moroctocog alfa (AF-CC) is bioequivalent to FLrFVII and the primary efficacy endpoint of this study has been met. This study also demonstrated that moroctocog alfa (AF-CC) PK characteristics remained unchanged after repeated use for 6 months. The use of moroctocog alfa (AF-CC) was efficacious in PTPs with severe hemophilia A for both prophylaxis treatment, as evidenced by a low annualized bleed rate, and on-demand treatment, as evidenced by a very high proportion of bleeds that resolved with 1 or 2 on-demand infusions.

- The primary safety endpoint of the study was also met. There was no clinical or laboratory evidence of neoantigenicity associated with moroctocog alfa (AF-CC) treatment. Transient, low-titer, clinically silent FVIII inhibitors were detected in only 2 of 94 subjects (2.1% incidence). The analysis applied in this study suggests the population (true) inhibitor rate for the test article is below the predefined acceptable value of 4.4%. The estimate of the 95% upper limit of the true inhibitor rate was 4.07%. No major safety signals were identified, and moroctocog alfa (AF-CC) was well tolerated.