

MEMORANDUM - Chairperson's Summary of Approval – XYNTHA

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

CHAIRPERSON'S SUMMARY OF APPROVAL

Date: 25 January 2008

To: The File of BLA 125264 and Pauline Cottrell

From: Nisha Jain & Tim Lee

Through: Basil Golding, M.D., Director, Division of Hematology

Subject: Approval of Wyeth's BLA for Antihemophilic Factor (Recombinant), Plasma/Albumin-Free [Moroctocg Alfa (AF-CC)] [XYNTHA]

This memorandum summarizes the review of the original biologics license application (BLA) for Antihemophilic Factor (Recombinant), Plasma/Albumin Free submitted by Wyeth Pharmaceuticals, Inc. (Wyeth). This product is also referred to as moroctocog alfa (AF-CC) in the BLA. The proposed trade name is XYNTHA, which is found acceptable by CBER's Advertising and Promotional Labeling Branch (APLB). The proposed indication of XYNTHA is for the control and prevention of bleeding episodes and for surgical prophylaxis in patients with hemophilia A.

FDA granted XYNTHA Orphan Drug designation.

The review committee consists of the following members:

Timothy Lee: Chairperson

Nisha Jain: Clinical Lead

Paul Buehler: Pharm/Tox

Pauline Cottrell and

Franklin Stephenson: RPM

Bhanumahti Kannan: BIMO

Dan Kearns: CMC and facility

Iftekhar Mahmood: Clinical Pharmacology

Jean Makie and
Catherine Miller: APLB
Boris Zaslavsky: Biostatistics.

Please refer to their individual review memoranda in the file for the detailed review of their respective disciplines.

The review committee finds the information provided in this application to be supportive of the safety, quality and effectiveness of this product for the proposed indication for the control and prevention of bleeding episodes and for surgical prophylaxis in patients with hemophilia A. Therefore, we recommend that this original BLA be approved.

BACKGROUND

Moroctocog alfa (AF-CC) is a purified B-domain deleted recombinant Factor VIII (FVIII) protein produced by recombinant DNA technology which is approved for treatment of hemophilia A. Moroctocog alfa (AF-CC) is produced using a modified version of moroctocog alfa, which eliminates the addition of all human and animal-derived proteins. This modified process also uses a chemically synthesized affinity ligand, TN8.2 in purification, replacing the murine monoclonal antibody Sepharose resin, thereby eliminating a potential risk of viral contamination.

Moroctocog alfa (AF-CC) is indicated for the control and prevention of bleeding episodes and surgical prophylaxis in patients with hemophilia A (congenital Factor VIII deficiency or classic hemophilia). Hemophilia A is an X chromosome-linked hereditary disorder of blood coagulation due to decreased levels of Factor VIII:C and results in bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. Replacement therapy with Factor VIII increases the plasma levels of Factor VIII, thereby enabling a temporary correction of the factor deficiency and the attendant bleeding tendencies.

The bulk drug substance of Antihemophilic Factor (Recombinant), Plasma/Albumin-Free is manufactured at ----- in -----, -----. The final formulated product is manufactured, filled, labeled, and packaged at -----, in ----- . This product is presented as a lyophilized powder in 250, 500, 1000 and 2000 IU/vial fill sizes, and supplied with a pre-filled syringe that delivers 4 mL of 0.9 % sodium chloride for the constitution of the product for injection.

The dating period for Antihemophilic Factor (Recombinant), Plasma/Albumin-Free shall be 24 months from the date of manufacture when stored at 2°C to 8°C. The dating period for your drug substance shall be -- months when stored at ----- The expiration date for the packaged product XYNTHA™ plus the 0.9 % sodium chloride diluent in a pre-filled syringe shall be dependent on the shortest expiration date of any component.

INDICATION

- Control and prevention of bleeding episodes and for surgical prophylaxis in Patients with Hemophilia A

TRADE NAME

The proprietary name of the product is XYNTHA™

ORPHAN DRUG STATUS

Orphan drug designation was granted in 1996 (application # -----)

PREA

PREA does not apply because of orphan drug status.

FINANCIAL DISCLOSURE

Financial disclosure forms have been submitted for all investigators.

CHEMISTRY MANUFACTURING AND CONTROLS (CMC)

Moroctocog Alfa (AF-CC) is a recombinant antihemophilic factor product manufactured with modifications to the currently licensed manufacturing process for ReFacto bulk drug substance (BDS). The BDS for moroctocog alfa (AF-CC) is manufactured at ----- --located in ----- . The modifications are implemented to eliminate the use of animal- and human-derived proteins in the manufacturing process, and are outlined as follows:

- -----

- Elimination of human serum albumin in the cell culture media
- Replacement of the monoclonal antibody Sepharose resin with a chemically-synthesized affinity ligand resin (TN 8.2)
- Introduction of a virus-retaining filtration step -----

In addition:

- The new reference standard used in the factor VIII (FVIII) potency assay was calibrated against the 7th FVIII International Standard (IS) using a one-stage clotting assay. This reference standard replaces the one that was calibrated against the 6th IS using a chromogenic substrate (CS) assay. Moroctocog alfa (AF-CC) will be released using a CS assay performed in accordance with the European Pharmacopoeia Assay of Blood Coagulation Factor VIII.

There were no major changes to the manufacturing process used to make the ReFacto final drug product (FDP) for moroctocog alfa (AF-CC). -----

-----.

Wyeth has provided information on testing of master cell bank (MCB) and working cell bank (WCB) for the manufacture of moroctocog alfa (AF-CC). Negative findings were recorded for the presence of mycoplasma and bacterial or fungal contaminants. No adventitious viruses were detected when samples were tested by any of the *in vitro* and *in vivo* tests. ----- showed cells to be of Chinese hamster origin, with no evidence of other contaminating species.

On the basis of these results, it was concluded that no detectable adventitious microbial or viral agents have been introduced into the BDDrFVIII (AF-CC) MCB and that no infectious retrovirus is present.

VIRAL TESTING AT OTHER STAGES OF PRODUCTION

[illegible]

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- _____

- A total of -- lots of FDP have been manufactured -----

- -----, Wyeth provided two tables to summarize the release data for these lots. All data met release specifications. Wyeth also presented representative -
-----, These data support the capability of Wyeth to manufacture a product of consistent quality.
- INSPECTION OF MANUFACTURING FACILITIES FOR XYNTHA

The pre-approval inspection of the manufacturing facilities for XYNTHA was waived based on criteria outlined in CBER SOPP 8410 "Determining When Pre-Licensing/Pre-Approval Inspections (PLI/PAI) are Necessary." The reasons are as follows:

- Wyeth holds U.S. license 3.
- The ----- facility was inspected within the last two years; the last biennial GMP inspection occurred on ----- (Dr. T. Lee was one of the inspectors) and was classified VAI. ----- was inspected from ----- and was classified VAI. ----- was inspected on ----- and was classified as NAI. A compliance check of all remaining ----- reveals no compliance actions related to any of the sites.
- The manufacturer is performing significant manufacturing, i.e., manufacture of the drug substance. However, the equipment, facilities, and processes have been inspected. There are no novel manufacturing issues associated with this submission. The changes in the licensed ReFacto® manufacturing process that are unique to this application are the establishment of -----

- -----, the use of albumin/plasma free cell culture, the replacement of the immunoaffinity column with a synthetic ligand column, and the addition of a virus filtration step.

- The most recent inspections associated with facilities involved in the manufacture of this product have been classified VAI or NAI.
- As noted, the application is for a process that eliminates the use of animal and human-derived proteins in the manufacturing of the product. As such, the manufacturing process, facilities, and controls do not represent any novel or significant manufacturing issues.

A -----, resulting from the -----
----- is used for production. This ---- was described in a supplement 103779/5463, and approved on July 6, 2007.

In summary, based on the information provided in the Biologics License Application STN 125264, the previous inspection history, and the overall compliance status of the license holder, the pre-approval inspection for the Wyeth facilities associated with this submission was waived.

From a CMC/product perspective, Wyeth's approach to establish the safety and effectiveness of moroctocog alfa (AF-CC) by demonstrating comparability to its currently licensed ReFacto product is acceptable. The components of the comparability program included an evaluation of operational process parameters, biochemical and functional characterization of the drug substance using release assays, structural and biophysical characterization of the API in the bulk drug substance and stability studies. The analytical methods and assessment criteria were chosen to ensure that the BDS of moroctocog alfa (AF-CC) and that of ReFacto have comparable identity, purity, potency, and quality. In addition, Wyeth also provided data to show that the FDP of moroctocog alfa (AF-CC) used in the non-clinical studies is comparable to ReFacto FDP and also representative of the moroctocog alfa (AF-CC) FDP used in clinical studies.

The CMC/product information provided in this application is supportive of the safety, quality and effectiveness of this product for the proposed indication for the control and prevention of bleeding episodes, and for surgical prophylaxis in patients with hemophilia A.

NONCLINICAL TOXICOLOGY

- Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted with XYNTHA to assess its mutagenic or carcinogenic potential. XYNTHA has been shown to be comparable to the predecessor product with respect to its biochemical and physicochemical properties, as well as its non-clinical in vivo pharmacology and toxicology. By inference, predecessor product and XYNTHA would be expected to have equivalent mutagenic and carcinogenic potential. The predecessor product has been shown to be non-genotoxic in the mouse micronucleus assay. No studies have been conducted in animals to assess impairment of fertility or fetal

development.

- Animal Toxicology and/or Pharmacology

Preclinical studies evaluating XYNTHA in hemophilia A dogs without inhibitors demonstrated safe and effective restoration of hemostasis. XYNTHA demonstrated a toxicological profile that was similar to the toxicological profile observed with the predecessor product. Toxicity associated with XYNTHA was primarily associated with anti-FVIII neutralizing antibody generation first detectable at 15 days of repeat dosing in high (1250 IU/kg/day) level dosed non-human primates.

CLINICAL PHARMACOLOGY

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 \pm 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 \pm 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 $AUC_{(0-\infty)}$ remained within 80% to 125%.

Figure 1

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

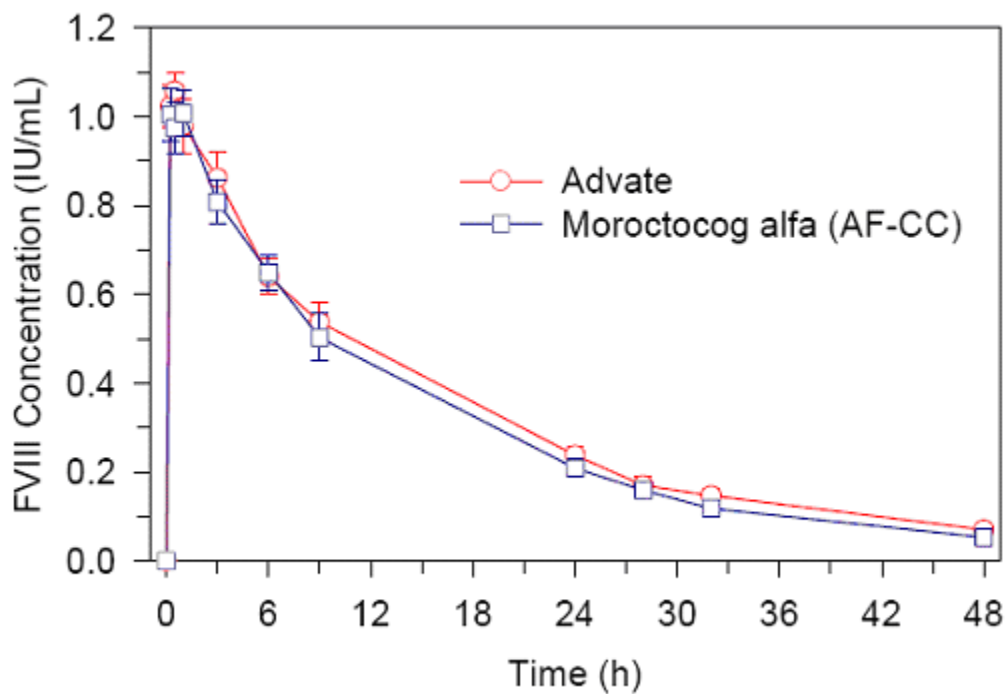


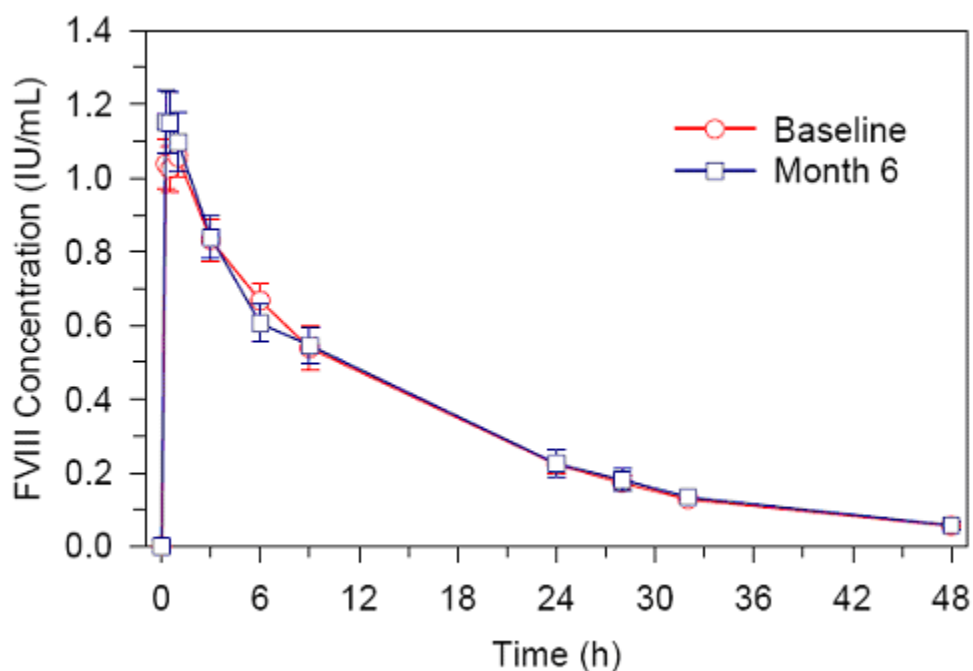
TABLE 2

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-∞) 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 Assessment:

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 $AUC_{(0-\infty)}$ 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)

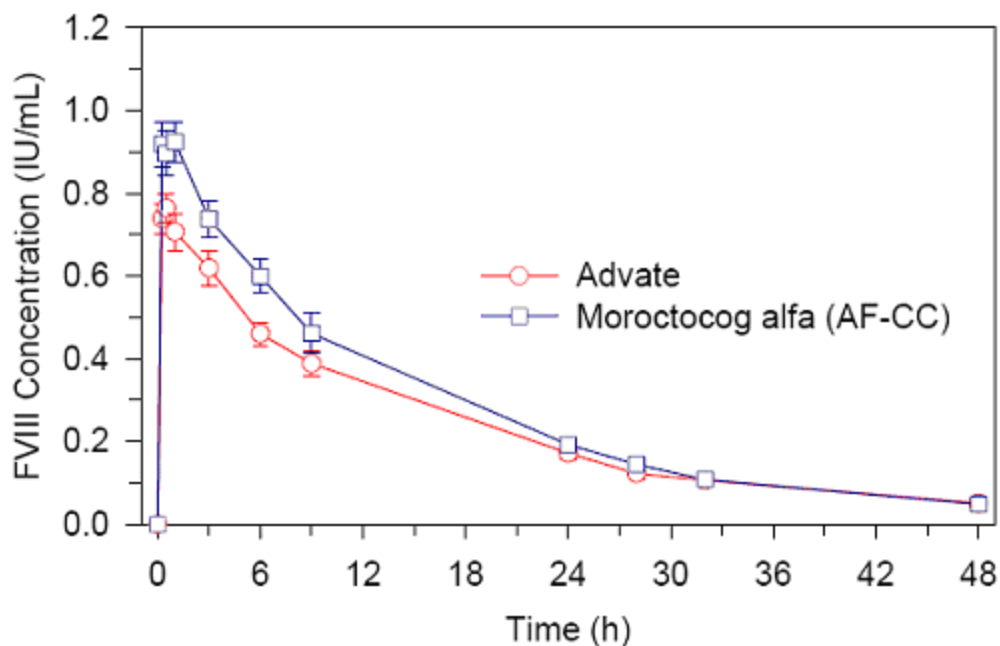


TABLE 4

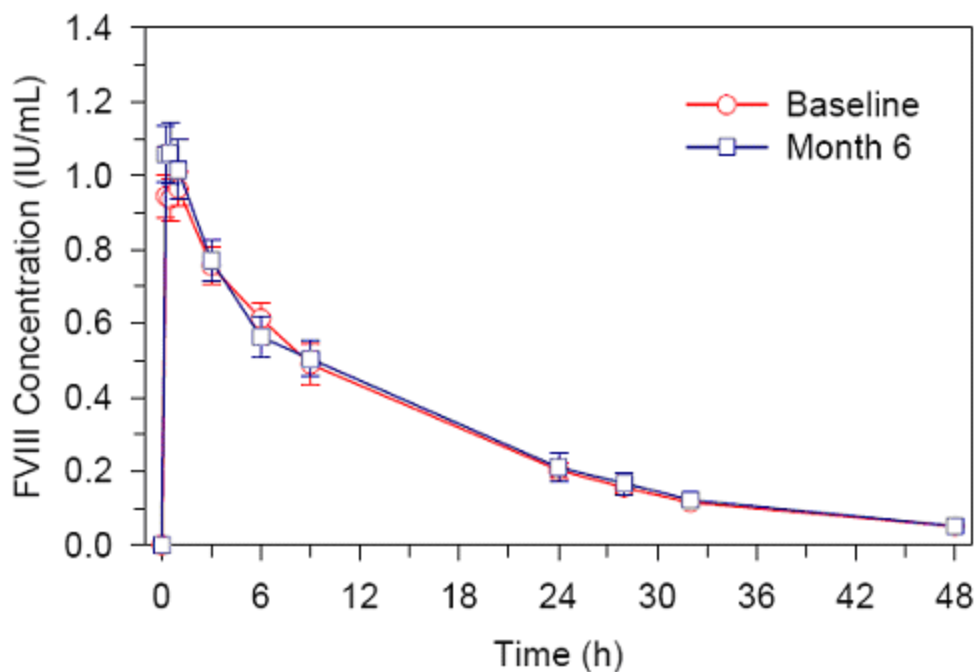
PK parameters for Moroctocog Alfa at baseline and month 6 in Previously Treated Patients With Hemophilia A (Based on Manufacturer's Potency Assessment)

Parameters	C _{max} (IU/mL)	AUC _(0-inf)	Half-life (hrs)	K-value	% Recovery
N	25	25	25	25	25
Baseline:					
Mean ± SD	1.12 ± 0.19	14.2 ± 5.5	11.8 ± 5.1	2.23 ± 0.39	105.5 ± 19.4
Range	0.593 – 1.413	4.7 – 25.0	6.4 – 33.9	1.19 – 2.83	53.4 – 132.0
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
Range	0.647 – 2.598	5.3 – 42.0	5.8 – 75.7	1.29 – 5.20	59.3 – 255.9
90% CI	96.4 – 119.59	93.88 – 115.37			

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)



Pharmacokinetics in children:

Although a study of XYNTHA in previously treated patients less than 6 years of age is currently ongoing, the sponsor has provided the following PK information in children between 12 to 16 years of age and this information has been incorporated in the labeling.

Pharmacokinetics of XYNTHA was studied in 7 previously treated patients 12-16 years of age. Pharmacokinetic parameters in these patients were similar to those obtained for adults after a dose of 50 IU/kg. For these 7 patients, the mean (\pm SD) C_{max} and AUC_{∞} were 1.09 ± 0.21 IU/mL and 11.5 ± 5.2 IU·h/mL, respectively. The mean clearance and plasma half-life values were 5.23 ± 2.36 mL/h/kg and 8.03 ± 2.44 hours (range 3.52 - 10.6 hours), respectively. The mean K value and *in vivo* recoveries were 2.18 ± 0.41 IU/dL per IU/kg and $112 \pm 23\%$, respectively.

Dispute Resolution:

There was a dispute on the number of pediatric patients enrolled in the study between the agency and the sponsor. This was finally resolved.

CLINICAL STUDIES

All the clinical studies conducted are listed below: Studies 3082B1-3050GL, 3082B1-306-GL and 3082-B1-307-GL were conducted with the old product and are analyzed and presented here only for safety. Studies 3082-B2-310-WW and 3082-B2-311-WW were conducted with the new product. Data from these two studies are presented and

analyzed for both safety and efficacy to support the licensure for the proposed indication.

Table 1-1: Clinical Studies of Moroctocog Alfa (AF-CC)

Protocol Number (Countries)	Study Design	Study Population	Test Product, Dosage Regimen, ³ Duration of Treatment	No. Enrolled Patients	Study Status/ Type of Report
<i>Clinical trials using drug substance manufactured in EU and intended for commercialization</i>					
3082B2-310-WW^b (Australia, Belgium, Finland, France, Germany, Hungary, Italy, New Zealand, Poland, Spain, Sweden, United States)	Double-blind, randomized, crossover PK period to assess BE of moroctocog alfa (AF- CC) and Advate®, followed by open-label period to evaluate efficacy and safety of moroctocog alfa (AF-CC) for use in prophylaxis and on- demand treatment of bleeding. Moroctocog alfa (AF-CC) PK at 6 months also evaluated for patients who completed PK period.	Male PTPs ≥12 years of age with moderately severe or severe hemophilia A (FVIII:C ≤1% in PK period; FVIII:C ≤2% in SE period) and ≥150 EDs to any FVIII product	PK period: Single doses of moroctocog alfa (AF-CC) and Advate following at least a 3-day washout period. Subjects returned after 6 months for a single dose of moroctocog alfa (AF-CC) SE period: Moroctocog alfa (AF-CC) for prophylaxis and on-demand treatment. Prophylaxis dosage regimen beginning at 30±5 IU/kg 3 times per week with dose escalations per protocol. On- demand regimen determined by investigator. At least 50 EDs in 6-month period.	94 94 M, 0 F 12-60 years 1 A, 4 O, 89 W	Completed/ Final
3082B2-311-WW^b (Australia, Austria, New Zealand, Poland, Romania, Russia, United States)	Open-label efficacy and safety study of moroctocog alfa (AF-CC) for use in surgical prophylaxis when administered by bolus or continuous infusion	Male PTPs ≥12 years of age with moderately severe or severe hemophilia A (FVIII:C ≤2%) and ≥150 EDs to any FVIII product undergoing elective major surgery	Moroctocog alfa (AF-CC) on an investigator-defined dosage regimen. At least 6 EDs following surgery.	8 8 M, 0 F 18-41 years 8 W	Ongoing/ Progress report
Protocol Number (Countries)	Study Design	Study Population	Test Product, Dosage Regimen, ⁴ Duration of Treatment	No. Enrolled Patients	Study Status/ Type of Report
<i>Clinical trials using drug substance manufactured in US that will not be commercialized</i>					
3082B1-305-GL (France, United States)	Double-blind, randomized, crossover study of BE of moroctocog alfa (AF-CC) and ReFacto® and PK of moroctocog alfa (AF-CC)	Male PTPs ≥12 years of age with severe hemophilia A (FVIII:C ≤1%) and ≥250 EDs to any FVIII product	Single doses of moroctocog alfa (AF-CC) and ReFacto following at least a 5-day washout period	30 30 M, 0 F 12-70 years 2 B, 3 H, 25 W	Completed/ Final
3082B1-306-GL (Canada, Denmark, France, Germany, Italy, United Kingdom, United States)	Open-label efficacy and safety study of moroctocog alfa (AF-CC) for use in routine prophylaxis, on- demand treatment of bleeding, and surgical prophylaxis. PK at 3 months also evaluated for patients who completed study 3082B1-305-GL.	Male PTPs ≥12 years of age ^c with severe hemophilia A (FVIII:C ≤2%) and ≥250 EDs to any FVIII product	Moroctocog alfa (AF-CC) dosage regimen as determined by investigator. At least 50 EDs.	110 110 M, 0 F 7-70 years 5 B, 6 H, 4 O, 95 W	Completed/ Final
3082B1-307-GL (Canada, France, Germany, Italy, United Kingdom, United States)	Open-label, long-term efficacy and safety study of moroctocog alfa (AF-CC) for use in prophylaxis, on- demand treatment of bleeding, and surgical prophylaxis. Recovery over time also evaluated.	Patients who completed study 3082B1-306-GL	Moroctocog alfa (AF-CC) dosage regimen determined by investigator. Two (2) years' treatment duration originally intended.	98 98 M, 0 F 7-70 years 4 B, 6 H, 4 O, 84 W	Terminated ⁴ / Abbreviated

Pivotal study synopsis: Protocol 308B2- 310- WW

The primary safety endpoint of this study was to determine the incidence rate of FVIII inhibitor associated with the use of XYNTHA in the study patient population. For the purposes of this study a patient was considered to have developed a positive inhibitor after they received study drug, if they had a titer of ≥ 0.6 BU/mL in a sample assayed at the central laboratory using the Nijmegen assay. Positive FVIII inhibitors were further categorized as low titer (≤ 5 BU/mL) or high titer (> 5 BU/mL).

The primary efficacy endpoint was to establish the PK equivalence of XYNTHA and a full-length recombinant FVIII (Advate) using the OS FVIII assay.

The secondary endpoints were to characterize the efficacy of the XYNTHA: efficacy response on a four point scale for treating spontaneous and traumatic bleeding episodes, efficacy response for on-demand and prophylaxis treatment, LETE, the consumption of XYNTHA (international units/kg) and to characterize the adverse events and the incidence of allergic reactions.

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 in routine prophylaxis and on-demand therapy in at least 81 previously treated patients (PTPs) with severe hemophilia A. Patients received a defined prophylaxis regimen for a minimum of 50 exposure days (EDs).

PK study:

Methodology

For PK, 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

Individual patient plasma FVIII concentrations were quantified using a validated OS clotting assay (Activated Partial Thromboplastin Time, or aPTT) with ---- Plasma Standard Calibrators, which were calibrated by the manufacturer against the --- -----

Inhibitor assessment:

Methodology:

Assessment of the presence of activity-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 < 0.6 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 XYNTHA test base. Patient serum samples were tested for the development of antibodies (both neutralizing and non-neutralizing) to XYNTHA using a validated ELISA. Patient serum samples were tested for the development of antibodies to CHO cell proteins derived from the cell line used in manufacturing of XYNTHA using a validated ELISA.

For the purposes of this study a patient was considered to have developed a positive inhibitor after they received study drug if they had a titer of ≥ 0.6 BU/mL in a sample assayed at the central laboratory using the Nijmegen assay. Positive FVIII inhibitors were further categorized as low titer or high titer. Low-titer inhibitors were defined as those positive inhibitors with a titer of ≤ 5 BU/mL in a sample assayed at the central laboratory using the Nijmegen assay. High-titer inhibitors were defined as those positive inhibitors with a titer of > 5 BU/mL assayed at the central laboratory using the Nijmegen assay.

Efficacy and Safety Statistical Methods

Analysis for Efficacy was done on ITT population (included all enrolled: randomized patients) and mITT (who received at least 1 dose of IP).

All safety analyses (other than the primary safety objective of FVIII inhibitor development rate) were performed on the ITT population.

Primary Safety Analysis: Assessment of Inhibitor (as described by the sponsor) The analysis of inhibitor formation was performed for the mITT population. A Bayesian statistical approach was employed to calculate the posterior probability that the population (true) inhibitor rate for the test article is below a predefined acceptable value. An acceptable value of 95% for this probability was selected to provide evidence that the clinical trial data predict inhibitor rates below the maximum population limit. This maximum (upper) population limit was set at a rate of 4.4%. These data were selected for development of a standard threshold since they correspond to relevant information about FVIII inhibitor incidence rates in PTPs, similar to those who are participating in this trial. The distribution for determination of this threshold (the standard distribution) was generated as the updated posterior distribution based on a prior of Beta [1,1] and using the data from the full-length FVIII studies noted above, where the empirical risk was 6/329.

Historical data used for standard distribution of Inhibitor incidence

Product	# of Inhibitor/ # of patients in the study
Kogenate (Bayer)	2/86
REcombine (Baxter)	2/69
Kogenate FS	1/76
Advate	1/103
Total	6/369

The standard distribution of Beta [7,324] was determined. Under these conditions the value associated with the 99th percentile, corresponding to a threshold value of 0.044, 4.4 %, was selected to target a threshold in the clinically acceptable upper threshold range of approximately 5%, in accordance with advice from FDA.

To determine the prior distribution for the test article, the actual prior distribution for B domain deleted FVIII product was considered. Using the inhibitor rate for 2 studies of in PTPs, the observed incidence was 4/223: 1 inhibitor in 113 patients who received ReFacto (predecessor product) in study 3082A1-300-WW and 3 inhibitors in 110 patients who received moroctocog alfa (AF-CC), XYNTHA prior to the current manufacturing change, in study 3082B1-306-GL. When updating the non-informative prior Beta [1,1] using these data from the previous studies with XYNTHA, the Beta [5,220] distribution is considered.

A 50% discount was selected to allow for exchangeability of the old data with the new data from the proposed clinical study. Thus, a prior of Beta [2.5, 110], that reflects a 50% discount of the previous B domain deleted FVIII data, was considered for analysis of new data generated in this study.

The posterior distribution of the inhibitor rate, given the data generated in the study, is also a beta distribution with parameters $a+x$ and $b+n-x$, where x is the number of observed inhibitors (and α and β are 2.5 and 110, respectively). From this distribution, the 95% probability that the data supports a value of the product's intrinsic inhibitor rate is calculated. For example, the observation of 2 inhibitors in a total of 81 study patients supports a probability of more than 95% that the true rate of inhibitors with XYNTHA is less than 4.4%. Similarly, studies of 14, 48 or 112 patients would support the observation of 0, 1, or 3 inhibitors, respectively, with at least 95% probability that the true rate was less than the upper threshold value of 4.4%. The observation of 2 inhibitors in 81 patients is the maximum number of inhibitors that may be observed in this clinical study population, under this statistical paradigm, and still be consistent with there being an inhibitor formation rate of less than 4.4%.

RESULTS:

Patient Characteristics:

94 subjects were enrolled and treated with at least one dose and all are included in the ITT population. From the 94 subjects enrolled, thirty-two (32) subjects participated in the

PK study and received at least 1 PK dose. Thirty-one (31) subjects completed both the first (PK1) and the second (PK2) assessments. Median age was 24 years (mean 27.7 and range 12-60 years). All had > 150 previous exposure days (ED) with baseline FVIII activity level of $\leq 2\%$.

Withdrawals:

Four (4) patients discontinued treatment early and the reasons are listed below: Patient -----: discontinued after 47 EDs (110 days on routine prophylaxis) for nonelective surgery.

Patient ----- (1 ED) and patient ----- (17 EDs and 51 days on routine prophylaxis): both withdrawn by the respective investigators due to non-compliance.

Patient -----: discontinued after 47 EDs (110 days on routine prophylaxis) for nonelective surgery.

Patient -----: withdrawn after 66 EDs (153 days on routine prophylaxis) due to the development of an inhibitor to FVIII. He had 38 EDs to moroctocog alfa (AF-CC) before the visit at which the inhibitor was detected and an additional 28 EDs after that visit and before he was withdrawn. Complete narrative on this patient is presented under safety analysis.

Primary Efficacy Analysis:

PK: As per Dr. Mahmood (see his review), analysis of the submitted data show that the PK of the two products (IP and Advate) are PK equivalent.

Primary safety analysis:

All 94 subjects enrolled in the study were evaluated for overall safety. However only 89 completed 50 exposure days to be considered for evaluation of the safety endpoint of inhibitor formation. Transient low-titer inhibitors were detected in 2 of 89 patients (2.24% of the study population) in this study. Both inhibitors were detected in clinically asymptomatic patients during routine protocol-specified surveillance tests.

Patient ----- was a 12-year-old Caucasian male with severe hemophilia A (FVIII activity <1% at screening), a reported history of 2050 EDs to FVIII, and a past medical history negative for a FVIII inhibitor; results from this patient's central laboratory assessments at visit 7 (month 3), after 38 EDs to the IP revealed a low-titer inhibitor of 0.9807 BU/ml. The patient was asymptomatic at this time.

Patient ----- was a 36-year-old Caucasian male with severe hemophilia A (FVIII activity <1% at screening), a reported history of 1100 EDs to FVIII, and a past medical history negative for a FVIII

inhibitor; results from his visit 10 (month 6) central laboratory assessment, after 81 EDs to the IP revealed a low-titer inhibitor of 1.2109 BU/ml.

For both patients, central laboratory results from inhibitor assays performed at visits immediately before and after inhibitor detection were negative. Neither patient exhibited clinical symptoms associated with the transient (single time point) low-titer FVIII inhibitor. There were no reports of LETE, no need for dose escalation, no instances of spontaneous breakthrough bleeds on prophylaxis, no bleeds within 72 hours of a prophylactic dose.

Bayesian methodology was employed in this study to calculate the probability that the population (true) inhibitor rate for the IP 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 $a+x$ and $b+n-x$, where x is the number of observed inhibitors, n is the number of patients analyzed (and α and β are 2.5 and 110)

Table 1

Bayesian Posterior Distribution of Inhibitor Rate							
				---Posterior Beta Distribution Characteristics---			
FVIII Inhibitor Nijmegen Result (BU/mL)	Number of Inhibitors	Number of Patients Analyzed	Observed Inhibitor Rate (%)	Alpha ^a	Beta ^b	Posterior Probability ^c	95% Upper Limit of Inhibitor Rate (%) ^d
≥0.6	2	89	2.13	4.5	202	0.9666	4.17

^a Prior alpha of 2.5 plus the number of observed inhibitors

^b Prior beta of 110 plus the number of patients analyzed minus the number of observed inhibitors

^c Posterior probability is the probability that the true inhibitor rate is less than the upper acceptable limit of 4.4 %. A posterior probability greater than 0.95 is 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 less than 4.4 % is deemed acceptable.

Secondary Efficacy analysis

All subjects started on prophylaxis regimen of 30 IU/kg 3 times a week. 7 dose escalations were prescribed for 6 patients during the course of the study: 2 escalations for patient ----- and single escalations for patients -----, and -----. 43/

94 (45.7%) reported no bleeding while on prophylaxis. Bleeding episodes that required treatment with FVIII and that occurred while the patient was on routine prophylaxis were considered in the calculation of the annualized bleeding rate (ABR). The median ABR for all bleeds for all patients was 1.9 (mean 3.9, range 0 to 42).

Fifty-three (53) of 94 patients received XYNTHA for on-demand treatment for a total of 187 bleeding episodes. Seven of these bleeding episodes occurred in subjects prior to switching to a prophylaxis treatment regimen. Hence, 180 bleeding episodes in 51 patients (88 spontaneous and 92 traumatic bleeds) were reported during routine prophylaxis. 61.1% (110 of 180 bleeds) occurred ≤ 48 hours after the last dose and 38.9% (70 of 180 bleeds) occurred > 48 hours after the last dose. The majority of bleeds reported to occur ≤ 48 hours after the last routine prophylaxis dose were traumatic (64 of 110 bleeds; 58.2%). 42 of 70 bleeds (60%) reported to occur > 48 hours after the last routine prophylaxis dose were spontaneous. 46 spontaneous bleeds As this study was not designed to evaluate the effectiveness of the prophylaxis regimen, presentation of this data is only for exploratory purposes.

Table 2

Total # of bleeding episodes (187, 180 bleeding episodes occurred in subjects on prophylaxis, 7 bleeds occurred in 2 subjects prior to prophylaxis)	
≤ 48 hours (Total=110/180)	> 48 hours (70/180)
Traumatic -64 (58.2%)	Traumatic- 28 (40%)
Spontaneous-46 (41.8%)	Spontaneous- 42 (60%)

Table 3

Time from infusion to new bleed

Time between last prophylaxis and start of bleed					
≤ 24 hours	$> 24 \leq 48$	$> 48 \leq 72$	> 72	Unknown ^a	Total BE
Spon traum	Spon traum	Spon traum	Spon traum	Spon traum	
13 20	33 44	24 12	18 16	3 4	187

^a Bleeds with unknown start time or bleeds in before the subject was started on prophylaxis dose of the safety and efficacy period of the study.

Abbreviations: Spon= spontaneous new bleed

Trau= traumatic new bleed

Table 4: Details on subjects with breakthrough bleeding occurring < 24 hours

[]

I-B interval: hours between previous routine prophylaxis infusion and start of bleeding episode

Subject ----- can be considered as true failure of the two prophylaxis regimens.

Subjects -----: the bleeds occurred within the ± 1 hour of 24 hours. If a conservative approach is taken, then the I-B interval for these subjects can be within the ± 1 hour of reporting error.

Subject ----- had a soft tissue bleed within 5.3 hours of his prophylactic dose. This subject had 6 breakthrough bleeds during the period of one year. 5/6 breakthrough bleeds were traumatic bleeding episodes. The subject experienced only one spontaneous bleeding episode during one year of prophylactic treatment which occurred within 5.3 hours of the prophylactic dose. Without knowing the subjects bleeding history with on demand therapy, it is not possible to comment on this single episode of spontaneous bleeding.

Subject ----- was most probably on inadequate prophylactic regimen. Two spontaneous bleeds were reported in a major joint within 28 days. The spontaneous bleed that occurred within 10 hours of the prophylactic dose, necessitated dose escalation to 45 IU/kg 3x/week resulting in no spontaneous bleeds for the remaining period of the study.

Additional secondary analysis:

Location of Bleeds:

187 bleeds in 53 patients were treated with on-demand infusions. 114 of 187 bleeds (61%) occurred in joints, 43 of 187 bleeds (23%) in soft tissue/muscle, 12/187 (0.064%): bleeds were mucosal bleeds and 18/187 (.096%) occurred at multiple sites at one time point (mostly joints and mucosal bleeding).

Treatment response using the hemostatic efficacy scale

Table 5: Treatment Response Measured Using a 4-Point Scale:

Summary of Response to Infusions to Treat New Bleeding Episode by Number of Infusions Needed for Resolution							
	-----Number of Infusions-----						
Response to 1st Infusion	Number of Subjects	1	2	3	4	> 4	Total Number of Bleeds
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

Summary of Response to Infusions to Treat New Bleeding Episode by Number of Infusions Needed for Resolution

Response to 1st Infusion	-----Number of Infusions-----						Total Number of Bleeds
	Number of Subjects	1	2	3	4	> 4	
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 Includes 1 infusion with commercial FVIII that occurred before routine prophylaxis began.							

The four point scale described above took into account pain relief (68% of patients used analgesics or anti- inflammatory drugs), a time course of 8 hours and # of infusions. The response to on-demand treatment was assessed using a 4-point scale described above. 70.6 % responses were rated as Excellent or Good. Forty-five (45) of 187 initial infusions (24.1%) to treat bleeds were rated moderate. Patients ----- and ----- contributed 18 of 45 moderate ratings and 2.7% of the initial infusion as no response. One subject received a commercially available product.

Subjects where dose escalation was needed based on prespecified escape criteria: All subjects started on prophylaxis regimen of 30 IU/kg 3 times a week. 7 dose escalations were prescribed for 6 patients during the course of the study: 2 escalations for patient ---- and single escalations for patients ----- and -----. 43/ 94 (45.7%) reported no bleeding while on prophylaxis. Fifty-seven (57/94; 60.6%) patients reported no spontaneous bleeding while on routine prophylaxis. Of these 57 patients, 14 patients reported traumatic bleeds but no spontaneous bleeds and 43 patients reported no bleeds of either type while on routine prophylaxis.

Lack of Effect:

In prophylaxis setting:

LETE in the prophylaxis setting was defined as a spontaneous bleed within 48 hours after a regularly scheduled prophylactic dose (which was not used to treat a bleed) of study drug in the absence of confounding factors. 56 spontaneous bleeds occurring in 29 subjects occurred within 48 hours of the prophylactic dose. If sponsor's definition of confounding factors is taken into account then 25 spontaneous bleeds in 13 subjects are identified. 14 of these events occurred in three subjects: ID -----

In 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 patient, in the

absence of confounding factors . Two (2) consecutive "no response" ratings were noted for 2 patients. LETE was considered for 1 patient. A confounder, trauma, (initial infusion >4 hours after onset of bleed) was present for the other patient.

Secondary Safety Analysis:

No deaths were reported in the study

Two (2) treatment-emergent SAEs were reported. Patient ----- reported an accidental injury (right maxillary sinus fracture), and patient ----- reported cellulitis of the knee. Both events were considered not related to the product and resolved. No subject developed anti CHO or Anti-TN8.2 antibodies. Hypertension was reported in 5 (5.3%) subjects, nausea in 6 subjects (6.4%) , Diarrhea in 5 (5.3%), Pharyngitis in 6 (6.4%). All the AEs were considered not related to the product.

Surgical prophylaxis study:

In this ongoing pivotal phase 3, open-label study XYNTHA will be assessed for effectiveness during peri-operative period in at least 25 evaluable PTPs with severe or moderately severe (FVIII:C \leq 2 %) hemophilia A undergoing major surgical procedures. Twenty-one subjects received XYNTHA by bolus injection (BI; 14 subjects) or by continuous infusion (CI; 7 subjects) at the physician's discretion to support surgical hemostasis followed by inpatient and outpatient postoperative care.

One subject received XYNTHA for a pre-surgery pharmacokinetic assessment only and had not undergone surgery. The 14 subjects treated by BI received a median total dose of 79,450 IU per subject (range 36,500 to 231,044 IU) over a median of 52 infusions per subject (range 17 to 72 infusions) during a median of 36 exposure days [ED] per subject (range 15 to 40 ED). The 8 subjects assigned to treatment by CI, including 1 subject who received only 1 dose for PK assessment, received a median total dose of 35,751 IU per subject (range 1,101 to 96,165) over a median of 9 ED per subject (range 1 - 64 ED).

An interim analysis was performed on the initial 21 of at least 25 planned evaluable subjects who had undergone major surgical procedures (14 total knee replacements, 3 synovectomies, 1 left ulnar nerve transposition release, 1 ventral hernia repair/scar revision, 1 knee arthroscopy, and 1 revision and debridement of the knee after a total knee replacement). For the 21 efficacy evaluable surgical subjects, investigator's ratings of efficacy at the end of surgery and at the end of the initial postoperative period were excellent or good for all assessments indicating that effective hemostasis was achieved with XYNTHA. All reported blood loss during the intra-operative and postoperative periods was rated normal with the exception of one patient who experienced abnormal post-surgical bleeding due to surgical trauma of the epigastric artery during a laparoscopic abdominal procedure, see Table 6 below.

Table 6: Summary of Hemostatic Efficacy

		Hemostatic Efficacy		Blood Loss	
Description of Surgical Procedure	BI or CI	End of Surgery Assessment	Day of Discharge/Day 6 Assessment	Normal Abnormal Intraop	Normal Abnormal Postop
Laparoscopic ventral incisional hernia repairs and scar revisions	CI	Excellent	Excellent	N	AB
Total right knee arthroplasty	BI	Good	Excellent	N	NR
Left ulnar nerve transposition release	BI	Excellent	Excellent	NR	NR
Right elbow synovectomy	BI	Good	Excellent	N	NR
Right knee synovectomy	BI	Excellent	Excellent	N	N
Left knee synovectomy	BI	Excellent	Excellent	N	NR
Total left knee replacement	BI	Excellent	Excellent	N	N
Total right knee replacement	BI	Excellent	Excellent	N	N
Total right knee replacement	BI	Excellent	Excellent	N	N
Total left knee replacement, followed by revision and debridement	BI	Excellent	Excellent	N	N
Total left knee replacement	BI	Excellent	Excellent	N	N
Total right knee replacement	BI	Excellent	Excellent	N	N
Total left knee replacement	BI	Excellent	Excellent	N	N
Total left knee replacement	BI	Excellent	Excellent	N	N
Total right knee replacement	BI	NESE	NESE	N	NR
Right hip replacement	CI	NESE	NESE	N	N
Total left knee replacement	CI	NESE	NESE	N	NR
Total right knee replacement	CI	Good	Good	N	NR
Right knee arthroscopy	CI	Excellent	Excellent	NR	NR
Total right knee	CI	Good	NR	N	NR

		Hemostatic Efficacy		Blood Loss	
Description of Surgical Procedure	BI or CI	End of Surgery Assessment	Day of Discharge/Day 6 Assessment	Normal Abnormal Intraop	Normal Abnormal Postop
replacement					
Total right knee replacement	CI	Good	NR	N	NR

Abbreviations: Intraop = intraoperative period; Postop = postoperative period; CI = continuous infusion; N = Normal; AB = Abnormal; BI = bolus injection; NESE = Not evaluable for surgical efficacy; NR = Not reported.

No patient had greater than 50 ml blood loss or required any blood transfusions.

Appendix I

Efficacy response on a four point scale as described by Tarantino et al:

Excellent:

Abrupt pain relief and/or improvement in signs of bleeding within approximately 8 hours after a single infusion

Good:

Definite pain relief and/or improvement in signs of bleeding within approximately 8 hours after an infusion, but possibly requiring more than one infusion for complete resolution

Moderate:

Probable or slight beneficial effect within approximately 8 hours after the first infusion; usually requires more than one infusion

No Response:

No improvement at all, or condition worsens.

Escape Criteria for increasing the dose of prophylactic regimen.

Routine prophylactic dosing was initiated using the same dosing regimen at "step 1" (30 ± 5 IU/kg 3 times a week) for all patients. The dose was prescribed by the investigator based on the actual potency on the label of the test article used, and the patient's most recent actual body weight as measured during the study. Predefined "escape" criteria provided rules for dose escalation to higher intensity dosing regimens, initially to step 2

(45 ± 5 IU/kg 3 times a week), and then to more frequent or higher doses as determined by the investigator. Escape criteria for escalating to a higher step (eg, step 1 to step 2) were either:

a) Two (2) spontaneous (atraumatic) bleeding episodes into major joints such as elbow, ankle or knee joint(s) or other target joints over a 4-week (28-day) period,

or

b) Three (3) or more spontaneous (atraumatic) bleeding episodes (eg, 1 joint and 2 soft tissue or other site) over a 4-week (28-day) period.

RECOMMENDATION

The review committee finds the information provided in this application to be supportive of the safety, quality and effectiveness of this product for the proposed indication for the control and prevention of bleeding episodes and for surgical prophylaxis in patients with hemophilia A. Therefore, we recommend that this original BLA be approved.