FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

Mid Cycle review memo:

DATE: 26-June-07

TO: STN 125264/0

SPONSOR: Wyeth Pharmaceuticals Inc.

PRODUCT: Antihemophilic Factor (Recombinant), Plasma/Albumin-free, ReFacto Xyntha

FROM: Nisha Jain, M.D., Clinical Review Branch, HFM-392

By Nisha Jain at 3:05 pm, Oct 30, 2007

SUBJECT: Mid-Cycle review of the BLA (STN 125264/0) for, Antihemophilic Factor (Recombinant), Plasma/Albumin-free, ReFacto AF

TO: Pauline Cottrell, Regulatory Project Manager, HFM-380

THROUGH: Toby Silverman, M.D., Chief, Clinical Review Branch, HFM-392

Cc: Tim Lee, Ph.D., Chairperson

> **APPROVED**
> *By Toby A. Silverman at 10:54 am, Oct 31, 2007*

SUMMARY:

The phase 3 pivotal has met its primary safety and efficacy endpoints. In the clinical trial the product has been shown to be PK equivalent to a licensed full length FVIII product, Advate. Two subjects out of 94 enrolled in the study developed inhibitor during the course of the study. The observation of 2 inhibitors in 81 patients was the maximum number of inhibitors pre specified in this clinical study population, under the Bayesian analysis method, in order to be consistent with an inhibitor formation rate of less than 4.4% (rate accepted for other licensed products).

REVIEW RESPONSIBILITIES:

CMC:	Tim Lee, Ph.D.
PK:	Ifthekar Mahmood, Ph.D.
Efficacy and Safety:	Nisha Jain, M.D.
Statistics:	Boris Zaslavsky, Ph.D

BIMO: Kannan Bhanu
DMPQ: Robert Stevenson
APLB: Catherine Miller and Jean Makie

TRADE NAME:
Wyeth's proposal for use of tradename of   was found to be acceptable when it was submitted in July 2006. Presently, Wyeth has been informed that the root name of "ReFacto" cannot be carried forward because the Investigational product (IP) is a new product:

. Wyeth will resubmit a trade-name to the Agency for consideration along with information relating to the choice and rationale of a trade name during the review of the BLA. In amendment #2 received on September 25, 2007, the sponsor has submitted the request to use the trade name "Xyntha" for FDA review.

ORPHAN DRUG STATUS:
Orphan drug designation was granted in 1996 (application #

PREA:
PREA does not apply because of orphan drug status.

INDICATION SOUGHT:
- Control and prevention of hemorrhagic episodes in patients with hemophilia A (congenital factor VIII deficiency or classic hemophilia)
- Surgical Prophylaxis in Patients with Hemophilia A
-

There is no data is submitted in the BLA to support the indication,
" Only two subjects during the study period developed   and were treated with escalated doses of the product.

REGULATORY HISTORY:

02 February 1998:	ReFacto BLA 98-0137 (STN 103779) submitted
06 March 2000:	Approved for treatment of spontaneous or traumatic bleeding in Hemophilia A
21 September 2001:	BB IND for Albumin-free product submitted
21 November 2001:	IND effective

Jan 04- Nov 2004:

Several communications with the Agency were conducted to address key aspects of the clinical development program: Because of the concern on safety, potential for increased rate of inhibitor formation than the licensed products, carry over of the Lack of Effect issue from ReFacto, FDA advised the sponsor to conduct a head to head comparative PK, safety and efficacy study with a licensed full length recombinant FVIII product.). The sponsor submitted the design of such a study 3082B2-310-WW as a special protocol assessment (SPA) (BB-IND-   SN 0074). In this submission Wyeth informed the FDA about new changes to the product:

Jan- March 2005:

Several telecons and correspondence relevant to the study design took place between the agency and the sponsor: Because of the   significant changes made to the product, the product was classified as a new product. The previous study design was no longer required. The new study should be designed to establish PK bioequivalence with a licensed full length recombinant FVIII product. Only if PK bioequivalence was not established then a comparative safety and efficacy study would be required. FDA also agreed to the concept of use Bayesian statistical methods to evaluate safety.

April- June 2005:   Several telecons to discuss the various parameters
                                        of Bayesian methods that could be used for the
                                        study.·
10 March 2006:   The FDA agreed to study proposals including
                                        statistical analysis plan.

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,[a] Duration of Treatment	No. Enrolled Patients	Study Status[c] Type of Report
Clinical trials using drug substance manufactured in EU and intended for commercialization					
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[d] 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[d] Progress report

Protocol Number (Countries)	Study Design	Study Population	Test Product, Dosage Regimen,[a] Duration of Treatment	No. Enrolled Patients	Study Status/ Type of Report
Clinical trials using drug substance manufactured in US that will not be commercialized					
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[d]/ Abbreviated

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Pivotal study synopsis: Protocol 308B2- 310- WW:
The primary safety endpoint of this study was to determine the incidence rate of FVIII inhibitors associated with the use of IP 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 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.

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

The secondary endpoints were to characterize the efficacy of the IP: 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 IP (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).

30/94 patients participated in a double-blind crossover study comparing the PK of IP to Advate. This crossover PK assessment occurred at the beginning of the study. After completing participation in the crossover PK assessment, these patients entered the SE period of the trial. Approximately 6 months later, all PK patients participated in the 6-month follow-up PK assessment.

Methodology:
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

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   BU/mL, are reported as 0.0 BU/mL. Plasma samples that had a positive inhibitor titer by the Nijmegen modification of the BA were then tested further using a normal plasma test base and a IP testbase. Patient serum samples were tested for the development of antibodies (both neutralizing and non-neutralizing) to IP using a validated ELISA. Patient serum samples were also tested for

the development of antibodies to CHO cell proteins derived from the cell line used in manufacturing of IP using a validated ELISA.

For PK, the manufacturer's actual labeled potency was used to calculate patient dosing. 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.

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: mITT) were performed on the ITT population.

PK Analysis: See PK reviewer's memo

Primary Safety Analysis: Development of Inhibitor
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
REcombinate (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 BDDrFVIII was also considered. Using the inhibitor rate for 2 studies of BDDrFVIII in PTPs, the observed incidence was 4/223: 1 inhibitor in 113 patients who received ReFacto in study 3082A1-300-WW and 3 inhibitors in 110 patients who received moroctocog alfa (AF-CC) in study 3082B1-306-GL. When updating the non-informative prior Beta [1,1] using these data from the previous moroctocog alfa studies, 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 moroctocog alfa data, is 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 moroctocog alfa (AF-CC) 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 eth 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 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.

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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.

<u>Primary Efficacy Analysis:</u>

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 bioequivalent.

<u>Primary safety analysis:</u>

All 94 subjects enrolled in the study were evaluated for safety. Transient low-titer inhibitors were detected in 2 of 94 patients (2.1% 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 aymptomatic 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,

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 the table below.

Bayesian Posterior Distribution of Inhibitor rate

FVIII Inhibitor Nijmegen Result (BU/mL)	Number of Inhibitors	Number of Patients Analyzed	Observed Inhibitor Rate (%)	---Posterior Beta Distribution Characteristics---			
				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 # of observed inhibitors
b. b. Prior beta of 110 plus # of patients analyzed –minus # of observed inhibitors
c. Posterior probability is the probability that the true inhibitor rate is less than the upper acceptable limit of 4.4%
d. 95% upper limit of the true inhibitor rate (maximum rate calculated with at least 95% probability) based on the posterior distribution.

Secondary Efficacy 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 Measured Using a 4-Point Scale:

Response to Infusion	First Infusion Per Bleed	Follow-Up Infusions	All Infusions
Excellent	44 (23.5)	12 (12.5)	56 (19.8)
Good	88 (47.1)	43 (44.8)	131 (46.3)
Moderate	45 (24.1)	38 (39.6)	83 (29.3)
No Response	5 (2.7)	3 (3.1)	8 (2.3)
Not Assessed	5' (2.7)	0 (0.0)	5' (1.8)
Total	187 (66.1)	96 (33.9)	283 (100)

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 000103 and 000105 contributed 18 of 45 moderate ratings and 2.7% of the initial infusion as no response. One subject received a commercially available product.

Other Secondary Endpoint Analysis for subjects on Prophylaxis:
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.

Annualized Bleeding rate:
180 bleeds were analyzed for secondary variable of ABR. 7 bleeds occurred in patients
prior to switching them to 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). 180 bleeding episodes in 51
patients (88 spontaneous and 92 traumatic bleeds) were reported during routine
prophylaxis. The median ABR for all bleeds for all patients was 1.9 (mean 3.9, range 0 to
42. The median ABR for spontaneous and traumatic bleeds individually was 0 for both
type of bleeds, with a mean ABR of 1.9 and 2.0 for spontaneous and traumatic bleeds,
respectively. 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. As this study was not designed to evaluate
the effectiveness of the prophylaxis regimen, presentation of this data is only for
exploratory purposes.

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%)

Time from infusion to new bleed

Time between last prophylaxis and start of bleed										
< 24hours		> 24 ≤ 48		> 48 ≤ 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

Details on subjects who had spontaneous bleeds in less than 24 hours after a prophylactic
dose:

Subject ID	Prescribed regimen:30IU/Kg/3x/week	Bleed location	I-B interval In hours	comments
	Y	Soft tissue	23	
	Y	Joint	22	
	Y	Joint	10	Changed to regimen B
	Y	Joint	23.5	
	Y	Joint	19.2	
	Two dose escalation: 30IU/Kg/3x/week: 18 days on regimen 45IU/Kg/3x/week: 10days 45IU/kg QOD: 133	Joint	22.5	True failure of the two prophylaxis regimen
	Yes	Joint	19.5	
	Y	Joint	23.4	
	Y	Joint	23.8	
	Y	Soft tissue	5.3	
	Y	Joint	20	
	Y	Joint	21	
	Y	Joint	23.5	

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/kg3x/week resulting in no spontaneous bleeds for the remaining period of the study.

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%) , Diarhea in 5 (5.3%), Pharyngitis in 6 (6.4%). All the AEs were considered not related to the product.

Comments to the sponsor:

1. For the indication, "Treatment of Hemophilia A in Certain Patients with Inhibitors to Factor VIII", please submit the data that supports it.

2. The   . Please resubmit a new tradename to the Agency for consideration along with information relating to the choice and rationale of this trade name.

3. For subjects   and   please submit the CRF and the reasons that led to the decision of non compliance by the investigators.

4. For subjects who experienced a spontaneous bleeding episode within 24 hours of the prophylactic dose, please provide your assessment as to the cause for the breakthrough bleeds.

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.