

Final Review Memo: Mid-Cycle Review – XYNTHA

MEMORANDUM

Food and Drug Administration
Center for Biologics Evaluation and Research

Final Review Memo:

DATE: 01 January 08

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

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, Chairperson

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 89 who completed 50 exposure days (94 subjects 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:

Daniel Kearns

APLB:

Catherine Miller and Jean Makie

Tox:

Paul Buehler

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 ----- because the Investigational product (XYNTHA) is a new product: ----- . Wyeth will resubmit a tradename to the Agency for consideration along with information relating to the choice and rationale of this 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. The trade name XYNTHA has been reviewed by APLB and found to be acceptable.

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 bleeding episodes and for surgical prophylaxis in Patients with Hemophilia A

FINANCIAL DISCLOSURE:

Financial disclosure forms have been submitted for all investigators.

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/ 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
<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 ^d / 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 ---- 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 004106 (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

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	89	2.13	4.5	202	0.9666	4.1

^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

<u>Time between last prophylaxis and start of bleed</u>					
< 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

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

Response to 1st 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 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

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