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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: ReFacto® Albumin-Free (AF) / Moroctocog Alfa (AF-CC)

PROTOCOL NO.: 3082B2-311 (B1831071)

PROTOCOL TITLE: An Open-Label Multicenter Study to Assess the Efficacy and Safety of B-Domain Deleted Recombinant Factor VIII (BDDrFVIII, ReFacto AF) in Patients With Hemophilia A Undergoing Elective Major Surgery

Study Centers: Ten (10) centers took part in the study and randomized subjects: 1 center each in Austria, Poland, Romania, the Russian Federation, and Sweden, 2 centers in New Zealand, and 3 centers in the United States (US).

Study Initiation Date and Final Completion Date: 06 April 2006 to 12 June 2008

Phase of Development: Phase 3

Study Objectives:

Primary Objective:

Demonstrate the safety and efficacy of ReFacto AF administered by bolus injection (BI) or continuous infusion (CI) during the perioperative management of subjects with hemophilia A undergoing major surgery.

Secondary Objectives:

- Characterize and compare the total and daily dose of ReFacto AF for both BI and CI.
- Characterize the pharmacokinetics (PK) of ReFacto AF in the subject population.
- Characterize the PK measurements required for surgical prophylaxis.
- Characterize the predicted and estimated blood loss and transfusion requirements in the study subject population.
- Characterize the variety of regimens used in those subjects treated by CI.
- Characterize subject compliance with prescribed regimens in the outpatient setting.

METHODS

Study Design: This study was an open-label multicenter study in subjects with severe or moderately severe hemophilia A undergoing elective major surgery, for which postoperative Factor VIII (FVIII) replacement therapy would be required, over a period of at least 6 consecutive days.

At the Screening Visit (Visit 1, approximately 10 weeks prior to surgery), before the Baseline Visit (Visit 2), the Investigator had to decide on using BI or CI for each subject's postoperative FVIII replacement therapy.

At Visit 2 (pre-surgical period and Baseline, approximately 4 weeks prior to surgery), baseline assessments (Table 1). During this visit subjects had an FVIII recovery assessment (for BI subjects) to estimate subject's FVIII recovery (Table 2), or a PK assessment (for CI subjects) to estimate the subject's recovery and clearance rate (Table 3). This baseline visit required a 3-days washout from all FVIII products. For each subject, the planned target FVIII activity level during and after surgery, the dose(s) and frequency on planed ReFacto AF infusions during surgery were recorded. Results from the FVIII recovery or PK assessment were utilized to plan the initial ReFacto AF dose and injection frequency (BI) or infusion rate (CI) used to achieve the planned target of FVIII activity. In addition, Investigator prospectively estimated blood loss and transfusion needs for each subjects

Between Visits 2 and 3, subjects were to continue to use their usual (prior to study) FVIII therapy, and not ReFacto AF, until Visit 3, the day of surgery.

At Visit 3 (day of surgery), subjects received ReFacto AF by BI or CI, and inpatient postoperative care was required for at least 2 days (48 hours) in BI subjects, and for at least 6 days (144 hours) in CI subjects. At least 12 subjects were to be treated by CI before conclusion of the study.

The schedule of activities is presented in Table 1 for the entire study, in Table 2 for Visit 2 (Day 1) recovery assessments in BI subjects, and in Table 3 for Visit 2 PK assessments in CI subjects.

Table 1. Study Flowchart 1

	Visit 1	Visit 2	Visit 3	Visit 4[a]	Visit 5[a]	Visit 6	Visit 998	Visit 999
Second Surgery (If Applicable)			**Visit 13**	**Visit 14**	**Visit 15**	**Visit 16**		
Procedure	**Screening (Approx. Week -10)**	**Pre-surgical Period/Baseline (Approx. Week -4)**	**Day of Surgery (Day 0)**		**Hospital Discharge**	**Interim Visit (If Necessary)[b]**	**Final Visit[c] (≤6 Weeks From Visit 3)**	**Final Study Contact (4 Weeks From Visit 998)**
			Postoperative Treatment (Inpatient)					
Informed consent process[d]	X							
Demographics	X							
Medical, medication, and hemophilia a history	X							
Collection of concomitant medication use		X	X	X	X	X	X	X
Decision of BI or CI	X							
Collection of adverse events		X	X	X	X	X	X	X
Physical examination	X					X	X	
Subject physical assessment[e]			X	X	X	X	X	
Vital signs	X	X[f]	X			X	X	
Body weight	X	X	X					
Serum chemistry	X						X	
CD4 count	X						X	
Hematology	X	X[f]					X	
Prothrombin time or INR	X							
PK/recovery assessment		X[f]						
Thrombosis risk screening[g]	X							
Hepatitis / HIV testing[h]	X							
Anti-CHO/Anti-TN8.2	X	X					X	
ReFacto AF administration		X[f]	X	X	X	X		
FVIII inhibitor assay[i]	X[j]	X[f]	X[j]				X	
Anti-FVIII ELISA	X	X	X				X	
FVIII activity (FVIII:C)[i]	X[j]	X[f, j]	X[j]	X[j]	X[j]		X	
Predicted and actual blood loss assessment		X	X	X	X			
Assessment of surgical hemostatic efficacy			X		X			

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	Visit 1	Visit 2	Visit 3	Visit 4[a]	Visit 5[a]	Visit 6	Visit 998	Visit 999
Second Surgery (If Applicable)			**Visit 13**	**Visit 14**	**Visit 15**	**Visit 16**		
Procedure	**Screening (Approx. Week -10)**	**Pre-surgical Period/Baseline (Approx. Week -4)**	**Day of Surgery (Day 0)**		**Hospital Discharge**	**Interim Visit (If Necessary)[b]**	**Final Visit[c] (≤6 Weeks From Visit 3)**	**Final Study Contact (4 Weeks From Visit 998)**
			Postoperative Treatment (Inpatient)					
Assessment of on-demand efficacy			X	X	X	X	X	
Description of planned therapeutic regimen		X[k]			X			
Description of changes to planned therapeutic regimen			X	X	X	X	X	
Dispense ReFacto AF				X[l]	X[l]	X		
Drug return and accountability						X	X	
Dispense subject diary	X	X		X[l]	X[l]	X		
Collect subject diaries		X	X			X	X	

AF = albumin-free; Approx = approximately; BI = bolus injection; CHO = chinese hamster ovary cells (host cell line); CI = continuous infusion; ELISA = enzyme-linked immunosorbent assay; FVIII = factor VIII; HCVAb = hepatitis C virus antibody; HBsAg = hepatitis B surface antigen; HBsAb = hepatitis B surface antibody; HBcAb = hepatitis C surface antibody; HAVAb = hepatitis A virus antibody; HIV = human immunodeficiency virus; INR = international normalized ratio; PK = pharmacokinetic.

a. For BI subjects who were discharged from the hospital on postoperative Days 3 through 6, the first 6 days after surgery corresponds to Visit 4 and Visit 5 took place on postoperative Day 7. For all BI subjects who remained hospitalized for >6 days and for all CI subjects, Visit 4 extended up to the day of hospital discharge (Visit 5).
b. Interim Visit (Visit 6) was approximately 1 to 2 weeks after Visit 5. If the Final Visit (Visit 998) was scheduled to occur <3 weeks after Visit 5, the Interim Visit (Visit 6) could have been waived.
c. The Final Visit (Visit 998) was scheduled to occur within 6 weeks following the Day of Surgery (Visit 3).
d. Notes to schedule of events: Signed and dated informed consent was obtained prior to performing any study procedure.
e. Subjects' physical assessment was performed to collect any relevant physical examination findings specific to surgery.
f. The procedures and collection of samples differs between BI and CI subjects; please see Table 2 and Table 3.
g. Thrombosis risk screening consisted of laboratory evaluation for deficiencies of Protein S, Protein C, Antithrombin (Antithrombin III), the presence of Factor V Leiden and the presence of the G to A transition at nucleotide 20210 in the Prothrombin gene (Prothrombin G20210A).
h. Hepatitis Panel included HCVAb, HBsAg, HBsAb, HBcAb, and HAVAb; HIV tests consisted of Anti-HIV 1 & 2 Ab screen.
i. Local non-protocol FVIII: C or FVIII inhibitor samples included a duplicate sample to be frozen and shipped to the central lab.
j. Duplicate samples were processed for analysis at the local and central laboratories; (all other testing during the study were processed at the central lab).
k. Done after recovery/PK data was available.

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Procedure	**Screening (Approx. Week -10)**	**Pre-surgical Period/Baseline (Approx. Week -4)**	**Day of Surgery (Day 0)**		**Hospital Discharge**	**Interim Visit (If Necessary)[b]**	**Final Visit[c] (≤6 Weeks From Visit 3)**	**Final Study Contact (4 Weeks From Visit 998)**
			Postoperative Treatment (Inpatient)					

l. ReFacto AF and subject Diaries were distributed at the time of discharge from the hospital (at Visit 4 for BI subjects with early discharge or at Visit 5 for all other subjects).

Table 2. Study Flowchart 2: Schedule of Events for Baseline Visit (Visit 2) Recovery Assessment for Bolus Injection Subjects

	Recovery Day 1					
Procedure		**Predose -2 - 0 hr**	**BI 0 - 2 min**	**15 min (±2 min)**	**30 min (±3 min)**	**1 hr (±6 min)**
Vital signs	3 day Washout	X				
Weight		X				
Test article administration			X			
CBC		X				
FVIII:C		X		X	X	X
FVIII Inhibitor		X				

BI = bolus injection; CBC = complete blood count; FVIII = factor VIII.

Table 3. Study Flowchart 3: Schedule of Events for Baseline Visit (Visit 2) Pharmacokinetic Assessment for Continuous Infusion Subjects

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

CBC = complete blood count; FVIII = factor VIII; PK = pharmacokinetic.

Number of Subjects (Planned and Analyzed): A minimum of 25 subjects was planned to be enrolled in the study. A total of 30 subjects (1 subject in Sweden, 2 subjects each in Austria and New Zealand, 4 subjects in Romania, 5 subjects in the US, and 8 subjects each in Poland and the Russian Federation) were enrolled and treated with at least 1 dose of ReFacto AF.

Diagnosis and Main Criteria for Inclusion: Male subjects, ≥12 years old, with severe to moderately severe hemophilia A (FVIII:C ≤2%), undergoing elective major surgery and requiring FVIII replacement and daily FVIII activity monitoring for at least 6 days postsurgery, previously treated with ≥150 exposure days (EDs) to any FVIII product, negative FVIII inhibitor test at Screening without past history of FVIII inhibitor activity, and able to comply with the mandatory 72-hour washout period and with the required inpatient length of stay (including ≥2 days for BI subjects and ≥6 days for all CI subjects), were eligible.

Study Treatment: ReFacto AF (ie, B-domain deleted recombinant Factor VIII [BDDrFVIII] produced in albumin-free cell culture [AF-CC], ReFacto AF [AF-CC]) was formulated as a sterile, nonpyrogenic, lyophilized powder preparation for intravenous (IV) injection. ReFacto AF was available in single-use vials containing the labeled amount of FVIII activity (IU), and each vial contained nominally 500 IU, 1000 IU, or 2000 IU per vial.

ReFacto AF at 50 ± 5 IU/kg was administered by IV BI or CI. Subjects assigned to the CI group were permitted to have intermittent BIs to supplement CI as needed. During the final postoperative period, CI subjects received ReFacto AF only by BI. Subjects assigned to the BI group were not permitted to have CI.

Efficacy and Safety Endpoints:

Efficacy Endpoint:

The primary efficacy endpoint for this study was a 4-point assessment of the hemostatic efficacy of ReFacto AF when used to support the subject during the surgical procedure. This assessment was for the experience during surgery through 1 hour after the end of the surgery. The assessment was determined by the Investigator or the surgeon after the end of the surgery on the day of surgery (Visit 3). The assessment was to be based on the comparison with the experience of similar subjects undergoing similar procedures.

Secondary Efficacy Endpoints:

- The efficacy as assessed by the Investigator at Visit 5 (Day 7 for BI subjects who had been previously discharged or the day of discharge from the hospital for all other BI and all CI subjects)

- The total and normalized consumption of ReFacto AF. The use of ReFacto AF will include but not be limited to the number of infusions and IU/kg dose per procedure, postoperative day and week

- Consumption of ReFacto AF per bleeding event, the number of bleeding episodes and response to treatment
- The pharmacokinetics of ReFacto AF in the subject population
- The incidence of less than expected therapeutic effect in both subject groups
- A comparison of the predicted and actual estimated blood loss and transfusion requirements
- The types of continuous infusion regimens and a comparison of planned regimens versus regimens actually used
- Subject compliance with prescribed outpatient regimens

Safety Endpoints:

- Adverse events (AEs) experienced by subjects on study were recorded along with the relationship, if any, to ReFacto AF
- The incidence of Factor VIII inhibitor formation in the subject population
- The incidence of thrombosis in the subject population
- The incidence of allergic reactions in the subject population

Safety Evaluations: Safety evaluations included routine physical and laboratory examinations, including assessment for FVIII inhibitor development, thrombosis and allergic reactions. All AEs and serious AEs (SAEs) were recorded. An independent data safety monitoring board could review safety data upon request of the sponsor.

Statistical Methods:

Efficacy: The Intent-to-Treat (ITT) population included all enrolled (randomized) subjects who received at least one dose of ReFacto AF. All safety and efficacy analyses were performed on the ITT population.

The hemostatic efficacy rating was summarized with frequencies and percentages for all subjects combined and for BI subjects and CI subjects separately. This analysis was performed on the ITT and efficacy evaluable populations.

The primary efficacy endpoint for this study was a categorical variable including the following outcomes: “excellent,” “good,” “moderate,” and “none.” These data were summarized in a tabulated format, ie, frequencies and percentages for each category were provided. The outcomes were also summarized for each of the subject populations (BI and CI groups).

All secondary efficacy endpoint analyses were performed on the ITT and efficacy evaluable populations. Secondary efficacy endpoints for this study were as follows:

- The outcomes of the efficacy assessment done by the Investigator at Visit 5 included "excellent," "good," "moderate," and "none." This endpoint was analyzed the same way as the primary efficacy endpoint.

- The consumption of ReFacto AF for the surgery indication was reported by the following distinct time periods: presurgery inpatient, intraoperative, initial postoperative period, and final postoperative period. The following variables were used to describe the consumption when appropriate: number of EDs, number of infusions, mean (IU/kg) per infusion, and total dose (IU).

- For treatment of a bleeding episode, the consumption of the study ReFacto AF was reported via number of infusions and mean dose (IU/kg). Bleeding episodes were too rare to permit a bleed-per-month analysis.

- The PK profile of ReFacto AF in the subject population was summarized by the subject treatment group (BI or CI). All the PK parameters including peak concentration (C_{max}), area under the concentration-time curve for 48 hours (AUC_t), incremental recovery: defined as the IU/dL of factor VIII: C increase per IU/kg of factor VIII infusion (K-value) and in vivo recovery (%) were reported.

- Numbers and percentages of subjects who experienced less-than-expected therapeutic effect (LETE) were provided for the total subject population. The incidences of LETE may be based on prophylaxis regimen, on-demand treatment, and low recovery.

- The predicted and actual estimated blood loss as well as the transfusion requirements were listed for clinical evaluation. These data were collected in a free text format and therefore no statistical analysis was planned.

- The CI regimen planned, eg, 4 IU/kg/hour, was compared with the actual regimen administered. Because BIs may be given to a subject during the CI period, and the actual CI regimen may change over time, these data were listed for clinical interpretation. No statistical analysis was performed.

- Subject compliance with prescribed outpatient regimens by the number of infusions and by the dose per infusion was provided.

Safety: Safety analysis was performed on the ITT population. AEs were coded by using a standard dictionary. Only treatment-emergent AEs (TEAEs) were included in the analysis. Numbers and percentages of subjects who experienced an AE were presented, regardless of the relationship to ReFacto AF. The incidence of FVIII inhibitor formation was considered an event of special interest. This was analyzed the same way as the other AEs.

RESULTS

Subject Disposition and Demography: A total of 30 subjects enrolled and were treated with at least 1 dose of ReFacto AF in the study and were included in the ITT population. One subject withdrew from the study early and did not undergo surgery. Because this subject received AF-CC for the PK assessment, he was counted in the ITT population. A total of 29 subjects underwent major surgery and completed the study. Of these 29 subjects who underwent surgery, 25 were included in the efficacy evaluable population.

Table 4 presents a summary of the demographic and baseline characteristics for the 30 subjects enrolled in the study. All subjects (100%) were white men. The median age was 34.5 years (mean 35.87 years; range, 18 to 53 years).

Table 4. Demographic and Baseline Characteristics of the Safety Population

Characteristic	Treatment		
	Bolus Injection (N = 22)	Continuous Infusion (N = 8)	Total (N = 30)
Age (Years)			
Mean (Standard deviation)	35.05 (9.51)	38.13 (8.54)	35.87 (9.22)
Minimum-maximum	18.00-53.00	24.00-48.00	18.00-53.00
Median	34.00	39.50	34.50
Sex n (%)			
Male	22 (100)	8 (100)	30 (100)
Race n (%)			
White	22 (100)	8 (100)	30 (100)
Ethnicity n (%)			
Non-Hispanic and Non-Latino	21 (100)	8 (100)	29 (100)
Missing	1	0	1
Weight (kg)			
n	22	8	30
Mean (Standard deviation)	76.68 (11.62)	75.99 (11.97)	76.50 (11.51)
Minimum-maximum	58.00-94.70	52.00-90.90	52.00-94.70
Median	79.05	80.00	79.05

N = total number of evaluable subjects; n = number of subjects.

Efficacy Results:

Primary Efficacy Endpoint: The primary efficacy endpoint was the Investigator's rating of the hemostatic efficacy of ReFacto AF at the end of surgery on the day of surgery (Visit 3, evaluating the experience during surgery through 1 hour after the end of surgery).

Of the 29 subjects who underwent surgery, 25 subjects were considered efficacy evaluable for surgical hemostasis. Three subjects received a prospectively planned infusion of auto-fresh frozen plasma (FFP), which rendered them unevaluable. One subject did not undergo surgery. One subject had a positive Nijmegen assay for inhibitor in a specimen obtained immediately prior to his surgery. Table 5 presents surgical procedures and efficacy outcomes for these 25 subjects.

Table 5. Listing of Surgical and Postsurgical Efficacy Outcomes for Efficacy Evaluable Subjects

			Hemostatic Efficacy		Transfusion (Yes/No)			Blood Loss (mL)				
Sr. No.	Description of Surgical Procedure	BI or CI	Visit 3	Visit 5	Predicted	Actual Intra-op	Actual Post-op	Predicted	Actual Intra-op	Normal Abnormal Intra-op	Actual Post-op	Normal Abnormal Post-op
1	Laparoscopic ventral incisional hernia repairs and scar revisions	CI	Excellent	Excellent	No	No	Yes	30	60	N	2400	AB
2	Right total knee arthroplasty	BI	Good	Excellent	Yes	No	No	600	400	N	0	-
3	Left total hip arthroplasty revision	BI	Good	Excellent	Yes	Yes	Yes	600	1500	N	0	-
4	Left knee arthroscopy with extensive synovectomy	BI	Excellent	Excellent	No	No	No	100	125	N	200	N
5	Release of l ulnar nerve transposition	BI	Excellent	Excellent	No	No	No	None	0	-	0	-
6	Synovectomy / right elbow	BI	Good	Excellent	No	No	No	60	200	N	0	-
7	Stapes plastic left ear	BI	Good	Good	No	No	No	2	2	N	0	-
8	Ankle arthrodesis	BI	Good	Excellent	No	No	No	100	150	N	0	-
9	Right knee synovectomy	BI	Excellent	Excellent	No	No	No	100	100	N	50	N
10	Left thigh pseudotumor excision	BI	Excellent	Excellent	No	No	No	200	150	N	0	-
11	Left hip arthroplasty	BI	Excellent	Excellent	No	No	Yes	1000	450	N	800	AB
12	Total left knee replacement	BI	Excellent	Excellent	Yes	No	No	1500	200	N	1050	N
13	Total right knee replacement	BI	Excellent	Excellent	Yes	No	No	1500	200	N	1260	N
14	Total right knee replacement	BI	Excellent	Excellent	No	No	No	1500	100	N	1170	N
15	Revision and debridement of left knee after total knee replacement	BI	Excellent	Excellent	Yes	No	No	1500	200	N	450	N
16	Total left knee replacement	BI	Excellent	Excellent	Yes	No	No	1500	200	N	1200	N
17	Total right knee replacement	BI	Excellent	Excellent	Yes	No	Yes	1500	200	N	1350	N
18	Total left knee replacement	BI	Excellent	Excellent	Yes	No	No	1500	200	N	1230	N
19	Total left knee replacement	BI	Excellent	Excellent	Yes	No	No	1500	200	N	980	N
20	Left elbow arthroscopy with synovectomy	BI	Excellent	Good	No	No	No	40	30	N	NA	AB
21	Right elbow arthroscopic synovectomy	BI	Excellent	Excellent	No	No	No	100	5	N	0	-
22	Total knee replacement of right knee	CI	Good	Excellent	No	Yes	No	1500	1050	N	0	-
23	Arthroscopy of right knee	CI	Excellent	Excellent	No	No	No	200	50	N	0	-
24	Total replacement of right knee	CI	Good	Excellent	No	Yes	No	1500	1350	N	0	-
25	Total knee replacement of right knee	CI	Excellent	Excellent	No	No	No	1500	500	N	0	-

AB = abnormal; BI = bolus injection; CI = continuous infusion; Intra-op = intraoperative; N = normal; Post-op = postoperative.

The most common surgical procedure was total knee replacement (11 subjects), followed by knee or elbow synovectomy (5 subjects). Nine subjects each had other procedures as shown in Table 5.

A summary of the ratings of hemostatic efficacy of ReFacto AF during the surgery at Visit 3 and for the initial postoperative period at Visit 5, by BI and CI treatment, is presented in Table 6 for the efficacy evaluable subjects.

Table 6. Summary of Surgical and Postsurgical Efficacy Outcomes

	Rating of Hemostatic Efficacy		
Visit	**Excellent**	**Good**	**Number of Subjects**
Treatment: Bolus Injection			
3	15 (75%)	5 (25%)	20
5	18 (90%)	2 (10%)	20
Treatment: Continuous Infusion			
3	3 (60%)	2 (40%)	5
5	5 (100%)	-	5

Of the subjects in the BI group, hemostatic efficacy at Visit 3 was rated as "excellent" for 75% (15/20) of subjects and "good" for 25% (5/20) of subjects. For the 5 efficacy evaluable subjects treated by CI, hemostatic efficacy at Visit 3 was rated as "excellent" for 60% (3/5) of subjects and "good" for 40% (2/5) of subjects. Overall, results at Visit 3 were excellent for 72% (18 of 25) and good for 28% (7 of 25) of the efficacy evaluable population.

Secondary Efficacy Endpoint:

Hemostatic Efficacy at Visit 5: The assessment of hemostatic efficacy was performed again at Visit 5 (Day7 for BI subjects who had been previously discharged or the day of discharge from the hospital for all other subjects) as a secondary endpoint. The Investigator's analysis was performed the same way as for the primary efficacy endpoint. Results are presented in Table 6.

Hemostatic efficacy at Visit 5 was rated as "excellent" for 90% (18/20) of subjects and as "good" for 10% (2/20) of subjects in the BI group. For the 5 subjects in the CI group, hemostatic efficacy at Visit 5 was rated as "excellent" for all subjects. Overall results at Visit 5 were excellent for 92% (23 of 25) of the efficacy evaluable population and good for 8% (2 of 25) of the efficacy evaluable population.

Three subjects, received infusions of auto-FFP during the intraoperative period. This was done per a preplanned routine practice at the study site and not in response to clinical outcomes. This practice was a major violation of the study protocol that prohibited the use of "medications that may interfere with coagulation" and rendered them non-evaluable for purposes of assessing surgical hemostatic efficacy of ReFacto AF. For these 3 subjects, all Investigator assessments of hemostatic efficacy at both Visit 3 and Visit 5 were "good" or "excellent." In addition, one subject developed an inhibitor that was detected by the central laboratory on the Visit 3 Nijmegen inhibitor assay, which disqualified him from the efficacy evaluable group. Visits 3 and 5 hemostatic efficacy assessments for this subject were both

rated "excellent" by the Investigator. Surgical and postsurgical efficacy outcomes for the ITT population, including the 4 non-evaluable subjects, are provided in Table 5.

Consumption of ReFacto AF: A summary of ReFacto AF consumption is presented in Table 7 for the BI group and Table 8 for the CI group.

The efficacy evaluable population received a cumulative total of 2,285,045 IU, inclusive of all doses until the final study Visit or until the time when a respective subject ceased to be evaluable. The median total dose per subject of ReFacto AF across all portions of the study for efficacy evaluable BI subjects was 83,002 IU; the median total dose per subject for efficacy evaluable CI subjects was 66,468 IU. The cumulative number of EDs was 759. The median number of EDs per subject was 26.5 (range 1 to 40 days).

For subjects treated by BI, the mean preoperative loading dose was 46.5 IU/kg (median 49.4 IU/kg; range 21.3 to 72.9 IU/kg). The mean total dose per subject was 86,772.4 IU (median 83,002; range 3380 to 231,044 IU). Of the 20 efficacy evaluable BI subjects, 1 required an intraoperative infusion (23.6 IU/kg; total dose of 2006 IU) of ReFacto AF to supplement the preoperative loading dose. In total, each subject treated by BI received a mean of 39.7 infusions overall. The mean number of EDs for BI subjects was 28.0 days (median 31 days; range 1 to 40 days).

For subjects treated by CI, the mean preoperative BI loading dose was 46.3 IU/kg (median 49.8 IU/kg; range 22.9 to 52.2 IU/kg). All 5 efficacy evaluable CI subjects completing surgery received intraoperative ReFacto AF by CI following the initial preoperative loading dose (mean 1181.2 IU/subject). No additional intraoperative BIs were reported; 1 CI subject received an on-demand treatment by BI (21.5 IU/kg; total dose of 1762 IU). The total dose per CI subject was 376,051 IU (median 66,468 IU; mean 53,721.6 IU; range 5286 to 96,251 IU); note that 1 CI subject only received an infusion for PK evaluation and did not elect to have surgery. The mean number of EDs for CI subjects was 20.6 days (median 22 days; range 2 to 37 days).

In addition, 3 of the 4 nonevaluable subjects also did not have additional infusions to supplement the loading dose.

Table 7. Summary of ReFacto AF Consumption: Bolus Injection Subjects, Efficacy Evaluable Population

Variable	Statistics	Pre-surgery: (PK/Recovery)	Inpatient Pre-op	Intra-operative	Initial Post-op	Final Post-op	On-Demand Infusions	Total
Total units (IU) per subject	Cumulative total	84344	85904	2006	668520	1049136	19085	1908994
	N (of subjects)	22	21	1	20	20	4	22
	Mean	3833.8	4090.6	2006.0	33426.0	52456.8	4771.3	86772.4
	Standard deviation	553.0	1082.2		12809.0	32282.2	1508.7	48055.5
	Median	3989	3842	2006	37999	47773	5023	83002
	Inter-quartile	3524, 4160	3518, 4160	2006, 2006	23787, 41944	33234, 60916	3515, 6028	67886, 110410
	Min, Max	2643, 4770	3009, 6834	2006, 2006	12480, 59074	16660, 163968	3009, 6030	3380, 231044
Range of infusion (IU)	Min, Max	2643, 4770	1346, 6018	2006, 2006	530, 5015	530, 5286	1003, 4020	530, 6018
Dose (IU/kg) per infusion	N (of infusions)	22	24	1	284	534	8	873
	Mean	49.7	46.5	23.6	30.9	25.4	28.0	28.4
	Standard deviation	3.6	12.8		12.1	12.0	13.9	13.0
	Median	50.0	49.4	23.6	30.4	23.4	24.4	24.4
	Inter-quartile	48.7, 51.6	39.4, 53.4	23.6, 23.6	21.9, 39.4	16.5, 34.1	17.0, 39.6	18.6, 36.5
	Min, Max	41.2, 55.5	21.3, 72.9	23.6, 23.6	8.4, 70.5	8.4, 58.3	12.2, 49.9	8.4, 72.9
Number of infusions/subject	Cumulative total	22	24	1	284	534	8	873
	N (of subjects)	22	21	1	20	20	4	22
	Mean	1.0	1.1	1.0	14.2	26.7	2.0	39.7
	Standard deviation	0.0	0.4		3.9	11.4	1.4	17.8
	Median	1	1	1	15	27	2	42
	Inter-quartile	1, 1	1, 1	1, 1	14, 17	19, 36	1, 3	32, 54
	Min, Max	1, 1	1, 2	1, 1	6, 19	7, 54	1, 4	1, 72
Exposure days per subject[a]	Cumulative total	22	21	1	153	432	8	615
	N (of subjects)	22	21	1	20	20	4	22
	Mean	1.0	1.0	1.0	7.7	21.6	2.0	28.0
	Standard deviation	0.0	0.0	-	1.5	6.8	1.4	11.0
	Median	1	1	1	7	23	2	31
	Inter-quartile	1, 1	1, 1	1, 1	7, 9	18, 28	1, 3	23, 36
	Min, Max	1, 1	1, 1	1, 1	6, 12	7, 32	1, 4	1, 40

Min = minimum; max = maximum; PK = pharmacokinetic; Pre-op = preoperative; Post-op = postoperative.

a. Inpatient pre-op, intra-operative, and initial post-op periods may occur on the same day, so the total exposure days may not be the sum of each period.

Table 8. Summary of ReFacto AF Consumption: Continuous Infusion Subjects, Efficacy Evaluable Population

Variable	Statistics	Pre-surgery: (PK/recovery)	Inpatient Pre-op	Intra-operative	Initial Post-op	Final Post-op	On-Demand Infusions	Total
Total units (IU) per subject	Cumulative total	26430	24632	5906	156489	160832	1762	376051
	N (of subject)	7	7	5	5	5	1	7
	Mean	3775.7	3518.8	1181.2	31297.8	32166.4	1762.0	53721.6
	Standard deviation	666.0	1005.0	662.0	6765.4	17598.9	-	34825.0
	Median	3524	3720	1047	30621	27556	1762	66468
	Inter-quartile	3524, 4405	2643, 4165	1025, 1380	28396, 34973	25794, 28192	1762, 1762	8570, 80000
	Min, Max	2643, 4405	1881, 4870	314, 2140	22286, 40213	16739, 62551	1762, 1762	5286, 96251
Range of BI infusion (IU)	Min, Max	2643, 4405	1811, 4870	-	-	465, 4405	1762, 1762	465, 4870
Dose (IU/kg) per BI infusion	N (of infusions)	7	7	-	-	103	1	118
	Mean	50.0	46.3	-	-	19.3	21.5	22.7
	Standard deviation	3.3	10.4	-	-	10.7	-	14.0
	Median	50.8	49.8	-	-	18.7	21.5	19.8
	Inter-quartile	47.2, 53.1	47.9, 51.7	-	-	12.2, 21.5	21.5, 21.5	12.2, 28.3
	Min, Max	44.6, 53.7	22.9, 52.2	-	-	6.5, 47.2	21.5, 21.5	6.5, 53.7
Number of bolus infusions	Cumulative total	7	7	-	-	103	1	118
	N (of subject)	7	7	-	-	5	1	7
	Mean	1.0	1.0	-	-	20.6	1.0	16.9
	Standard deviation	0.0	0.0	-	-	6.7	-	11.5
	Median	1	1	-	-	18	1	19
	Inter-quartile	1, 1	1, 1	-	-	17, 26	1, 1	2, 28
	Min, Max	1, 1	1, 1	-	-	13, 29	1, 1	2, 31
Exposure days per subject	Cumulative total	7	7	5	37	100	-	144
	N (of subject)	7	7	5	5	5	-	7
	Mean	1.0	1.0	1.0	7.4	20.0	-	20.6
	Standard deviation	0.0	0.0	0.0	0.9	7.2	-	14.0
	Median	1	1	1	8	18	-	22
	Inter-quartile	1, 1	1, 1	1, 1	7, 8	14, 26	-	2, 34
	Min, Max	1, 1	1, 1	1, 1	6, 8	13, 29	-	2, 37

Table 8. Summary of ReFacto AF Consumption: Continuous Infusion Subjects, Efficacy Evaluable Population

Variable	Statistics	Pre-surgery: (PK/recovery)	Inpatient Pre-op	Intra-operative	Initial Post-op	Final Post-op	On-Demand Infusions	Total
CI duration (hrs) per subject	Cumulative total	-	1	18	748	-	-	767
	N (of subject)	0	4	5	5	0	0	6
	Mean	-	0.2	3.6	149.7	-	-	127.9
	Standard deviation	-	0.1	1.5	15.0	-	-	63.8
	Median	-	0	4	157	-	-	152
	Inter-quartile	-	0, 0	3, 4	138, 162	-	-	134, 164
	Min, Max	-	0, 0	2, 6	129, 162	-	-	0, 166
CI rate (IU/kg/hr) per subject	Cumulative total	-	13	19	14	-	-	16
	N (of subject)	0	4	5	5	0	0	6
	Mean	-	3.4	3.9	2.7	-	-	2.7
	Standard deviation	-	1.2	0.7	0.8	-	-	0.8
	Median	-	3	4	3	-	-	2
	Inter-quartile	-	2, 4	4, 4	2, 3	-	-	2, 3
	Min, Max	-	2, 4	3, 4	2, 4	-	-	2, 4

Inpatient Pre-op and Intra-operative periods, Initial post-op period may occur on the same day, so the total exposure days may not be the sum of each period.
AF = albumin free; BI = bolus injection; CI = continuous infusion; min = minimum; max = maximum; PK = pharmacokinetic; Pre-op = preoperative; Post-op = postoperative.

Assessment of Blood Loss and Transfusion Requirements: Before surgery; the Investigator predicted and recorded estimates of intraoperative blood loss and intraoperative transfusion needs of both BI and CI subjects. In their estimates, Investigators assumed the surgery would be completed without major complications and could use their institution's standard transfusion guidelines, if available. This estimate was compared with the actual recorded blood loss during surgery and any transfusions occurring in surgery.

Blood loss was assessed for the intra- and postoperative periods (Table 5). As predicted by the Investigator, 24 of the efficacy evaluable subjects had intraoperative blood loss; for all efficacy evaluable subjects, intraoperative blood loss was rated normal. A total of 13 efficacy evaluable subjects had postoperative blood loss; in 10 cases the postoperative blood loss was rated normal, 1 case was rated abnormal due to hemorrhage following surgical trauma to the epigastric artery, 1 due to an 800 mL blood loss after hip replacement surgery, and 1 after an elbow synovectomy but the blood loss could not be measured by the Investigator. Nine of 25 efficacy evaluable subjects were prospectively predicted to require transfusions during the intraoperative period; of these 9, only 1 received a transfusion. Two of the 16 efficacy evaluable subjects, predicted not to require intraoperative transfusion, received transfusions with packed red blood cells (PRBCs); for both, blood loss was reported as normal. During the postoperative period, 4 efficacy evaluable subjects received transfusions, including 1 subject who received PRBCs following excessive hemorrhage associated with trauma to the epigastric artery during surgery. Three subjects received infusions of FFP during the intraoperative period.

Pharmacokinetics: Of the total 30 subjects, 16 had a measurable preinfusion FVIII concentration (up to a maximum of 0.154 IU/mL). A summary of PK parameters are shown in Table 9. For both the BI and CI subjects, the mean (± SD) K-value was 2.11 (± 0.43) IU/dL per IU/kg, and the mean (± SD) in vivo recovery value was 101% (± 20%).

Table 9. Pharmacokinetic Parameter Estimates in BI and CI Subjects With Hemophilia A After a 2-Minute IV Infusion of 50 IU/kg of ReFacto AF at Visit 2

Parameter	Units	n	Mean ± Standard Deviation
C_{max}	IU/mL	30	1.06 ± 0.21
K-value	IU/dL per IU/kg	30	2.11 ± 0.43
Recovery	%	30	101 ± 20
AUC_{inf}	IU·hr/mL	8[a]	16.0 ± 5.2
Cl	mL/hr/kg	8[a]	3.48 ± 1.25
$t_{½}$	hr	8[a]	16.7 ± 5.4
V_{ss}	mL/kg	8[a]	69.0 ± 20.1

AUC_{inf} = area under the plasma concentration-time curve from time 0 to infinity; CI = continuous injection, Cl = clearance; C_{max} = peak concentration; K-value = incremental recovery; $t_{½}$ = terminal-phase elimination half-life; V_{ss} = steady-state volume of distribution.
a. CI subjects only.

Planned Continuous Infusion Regimens: The CI group consisted of 8 subjects at 2 study sites (01 and 27). For all CI subjects the initial rate of CI was informed by study site standard of care rather than the clearance calculated from the respective subject's baseline PK

assessment. Both study sites chose to use the large-volume/low-concentration solution method for preparing the infusion; however, the diluent was different at the 2 sites.

Table 10 displays the method of preparation and delivery information for the sites. In the 7 CI subjects who underwent surgery (all of whom were in the ITT population, and 5 of 7 were efficacy evaluable), the infusion concentrations were lower than the protocol-specified limit on at least 1 occasion. As well, for 5 subjects, the infusion rate (mL/hour) was lower than the protocol-specified limit on at least 1 occasion. Therefore, there was the potential for compromise in delivery of ReFacto AF to these CI subjects.

Table 10. Preparation of ReFacto AF Continuous Infusion for the Surgery

Study Site	01	27
Number of subjects	1	7[a]
Method of dilution	5% dextrose	Normal saline
Method of delivery	Mini-pump / Computerized ambulatory drug delivery	Simple gravity intravenous pole
Diluted drug concentration (range)	8.9-19.4 IU/mL	7.0-14.3 IU/mL
Intraoperative infusion rate:		
Mean	3.7 IU/kg/hr	
Standard deviation	0.9	
Min, Max	(2, 4) IU/kg/hr	

AF = albumin free; FFP = fresh frozen plasma.
a. Five of these subjects were in the efficacy evaluable population, and 2 were not (by reason of auto-FFP treatment).

Bleeding Episodes: Table 11 presents a listing of bleeding episodes that were treated with ReFacto AF. A total of 10 bleeding episodes in 7 subjects were reported in the postoperative setting and required on-demand treatment. The range of infusion doses was 12.2 to 49.9 IU/kg. Of these 10 bleeding episodes, 7 were traumatic due to injury, in 3 instances affecting the joint that had undergone surgery. Three episodes reflected spontaneous new bleeding episodes. Nine episodes each were treated with a single infusion of ReFacto AF, and 1 bleeding episode of traumatic origin required a follow-up (second infusion); thus all bleeding episodes resolved with 1 (90%) or 2 (10%) infusions. All but 1 of these episodes occurred during the final postoperative period (after Visit 5) and therefore occurred in the outpatient setting). One traumatic bleeding episode occurred during the initial postoperative period (after surgery but before discharge from the hospital) when the subject accidentally bumped the operated leg against the bed.

The response to treatment was rated “excellent” by the Investigator for 2 and by the subject for 5 of the initial infusions, and “good” for the remaining 3 initial infusions (1 by the Investigator and 2 by the subject) used for on-demand treatment of these respective bleeding episodes. Most of those bleeding events were treated pharmacologically.

Table 11. Listing of Bleeding Events Treated With ReFacto AF

Sr. No.	Study Period	Start Date /Time	Inf. Reas.[a]	Site type	Site	Location	Comment	Start Date /Time	Dose (IU/kg)	Response/ Assessor[b]
1	Final post-op	19Dec07/ 17:20	INJ	Soft tissue/ muscle	Arm and hand	Left	Trauma	19Dec07/ 18:45	35.5	E/SG
2	Final post-op	19Dec07/ 16:30	INJ	Joint	Ankle	Right	Posttrauma: self injury during regular home activities	19Dec07/ 17:40	24.4	E/SG
		25Dec07/ 18:15	INJ	Joint	Knee	Right	Posttrauma: self injury during regular home activities	25Dec07/ 19:30	24.4	E/SG
		26Dec07/ 17:45	INJ	Soft tissue/ muscle	Wrist	Left	Posttrauma: self injury during regular home activities	26Dec07/ 18:30	12.2	E/SG
		31Dec07/ 19:05	INJ	Joint	Hand	Right	Mistake – subject self-injured right hand	31Dec07/ 20:15	12.2	E/SG
3	Final post-op	22Oct07/ 15:00	SNB	Soft tissue/ muscle	Arm	Right	None	22Oct07/ 15:30	49.9	G/SG
4	Final post-op	28Apr08/ 5:00	INJ	Soft tissue/ muscle	Mouth	Left	Subject was eating beef jerky evening before. Awakened with evidence of bleeding	28Apr08/ 12:05	43.8	G/SG
			F/U	Soft tissue/ muscle	Mouth	Left		29Apr08/ 20:28	21.9	E/SG
5	Initial post-op	25Mar07/ 19:45	INJ	Joint	Knee	Right	After trauma (subject bumped the operated leg against the bed)	25Mar07/ 20:15	14.0	E/IN
6	Final post-op	10May07/ 19:45	SNB	Joint	Knee	Left	None	10May07/ 20:30	17.9	G/IN
7	Final post-op	13Jun07/ 6:30	SNB	Joint	Knee	Right	None	13Jun07/ 10:20	21.5	E/IN

AF = albumin free; Inf = infusion; Op = operative; Reas = reason.

a. Infusion reason: SNB = spontaneous new bleeding episode; INJ = New bleeding episode due to injury; F/U = follow-up infusion.

b. Response: E = excellent; G = good; M = moderate; N = no response; U = unknown. Assessor: SG = subject/guardian; IN = Investigator; UN = unknown.

Less-Than-Expected Therapeutic Effect (LETE): There were 5 reports of possible LETE in 4 subjects during this study. Three (3) of the events were associated with confounding factors; thus there were 2 true events of LETE, both in the prophylactic setting.

Measurements of Treatment Compliance: In the outpatient setting, 4 subjects were noted to have an interval in time where the mean actual dose administered was >20% discordant from a single prescribed regimen. In addition, 3 of the 4 subjects were identified as those who, in aggregate, were >20% discordant from their overall mean planned dose during the final postoperative period.

Fourteen (14) subjects had an interval of time in which the frequency of infusions was >20% discordant from a single prescribed regimen.

Safety Results:

A summary of all treatment emergent AEs (TEAEs) by severity, regardless of causality, is presented in Table 12.

Twenty-six (26; 86.7%) subjects reported at least 1 TEAE during the study. The most frequent TEAEs (reported in ≥10% of subjects) were fever (13; 43.3%), local reaction to procedure (11; 36.7%), anemia (9; 30.0%), infection (5; 16.7%), headache (4; 13.3%), nausea (4; 13.3%), accidental injury (3; 10.0%), flu syndrome (3; 10.0%), hypertension (3; 10.0%), thrombocythemia (3; 10.0%), and upper respiratory infection (3; 10.0%). Most TEAEs (53.3%) were mild in intensity, 30% were moderate, and 1 (hypovolemia) was severe. In addition, there was 1 TEAE considered to be life-threatening (postoperative bleeding).

No TEAEs were deemed related to treatment with ReFacto AF by the Investigator.

Table 12. Number (%) of Subjects With Treatment-Emergent Adverse Events

	Maximum Severity Grade[a]				
Body System[b] Event	**Mild**	**Moderate**	**Severe**	**Life-threatening**	**All**
Any event	16 (53.3)	9 (30.0)	0	1 (3.3)	26 (86.7)
Body as a whole					
Fever	10 (33.3)	3(10.0)	0	0	13(43.3)
Infection	2 (6.7)	3(10.0)	0	0	5(16.7)
Headache	4(13.3)	0	0	0	4(13.3)
Flu syndrome	2(6.7)	1(3.3)	0	0	3(10.0)
Accidental injury	3(10.0)	0	0	0	3(10.0)
Chills	2(6.7)	0	0	0	2(6.7)
Asthenia	0	1(3.3)	0	0	1(3.3)
Cellulitis	0	1(3.3)	0	0	1(3.3)
Pain	0	1(3.3)	0	0	1(3.3)
Back pain	1(3.3)	0	0	0	1(3.3)
Non-specified drug reaction	1(3.3)	0	0	0	1(3.3)
Cardiovascular system					
Hypertension	2(6.7)	1(3.3)	0	0	3(10.0)
Hemorrhage	0	0	0	1(3.3)	1(3.3)
Hypovolemia	0	0	1(3.3)	0	1(3.3)
Tachycardia	0	1(3.3)	0	0	1(3.3)
Hypotension	1(3.3)	0	0	0	1(3.3)
Pallor	1(3.3)	0	0	0	1(3.3)
Digestive system					
Nausea	2(6.7)	2(6.7)	0	0	4(13.3)
Vomiting	1(3.3)	1(3.3)	0	0	2(6.7)
Abdominal distension	0	1(3.3)	0	0	1(3.3)
Constipation	1(3.3)	0	0	0	1(3.3)
Diarrhea	1(3.3)	0	0	0	1(3.3)
Jaundice	1(3.3)	0	0	0	1(3.3)
Mouth ulceration	1(3.3)	0	0	0	1(3.3)
Hemic and lymphatic system					
Anemia	5(16.7)	4(13.3)	0	0	9(30.0)
Thrombocythemia	1(3.3)	2(6.7)	0	0	3(10.0)
Leukocytosis	0	1(3.3)	0	0	1(3.3)
Metabolic and nutritional					
Peripheral edema	1(3.3)	1(3.3)	0	0	2(6.7)
Bilirubinemia	0	1(3.3)	0	0	1(3.3)
Musculoskeletal system					
Arthralgia	1(3.3)	0	0	0	1(3.3)
Plantar fasciitis	1(3.3)	0	0	0	1(3.3)
Nervous system					
Hypesthesia	1(3.3)	0	0	0	1(3.3)
Memory impairment	1(3.3)	0	0	0	1(3.3)
Paresthesia	1(3.3)	0	0	0	1(3.3)
Respiratory system					
Upper respiratory infection	2 (6.7)	1 (3.3)	0	0	3 (10.0)
Cough increased	0	1 (3.3)	0	0	1 (3.3)
Rhinitis	0	1 (3.3)	0	0	1 (3.3)
Skin and appendages					
Vesiculobullous rash	2 (6.7)	0	0	0	2 (6.7)
Rash	1 (3.3)	0	0	0	1 (3.3)

Table 12. Number (%) of Subjects With Treatment-Emergent Adverse Events

Body System[b] Event	Maximum Severity Grade[a] Mild	Moderate	Severe	Life-threatening	All
Special senses					
Abnormal vision	1 (3.3)	0	0	0	1 (3.3)
Ear disorder	1 (3.3)	0	0	0	1 (3.3)
Urogenital system					
Scrotal edema	0	1 (3.3)	0	0	1 (3.3)
Hematuria	1 (3.3)	0	0	0	1 (3.3)
Kidney calculus	1 (3.3)	0	0	0	1 (3.3)
Oliguria	1 (3.3)	0	0	0	1 (3.3)
Adverse event associated with miscellaneous factors					
Local reaction to procedure	8 (26.7)	3 (10.0)	0	0	11 (36.7)

AEs and SAEs are not separated.
AE = adverse event; SAE = serious adverse event.
a. Only the events with the worst severity are tabulated.
b. Body system totals are not necessarily the sum of the individual events because a subject may report 2

Table 13 presents all reported treatment-emergent hemophilia events by severity, regardless of causality. Out of 5 hemophilia events, 3 events (2 events of factor VIII inhibition and 1 event of hemorrhage) were deemed by the Investigator to be at least possibly related to study drug.

Table 13. Number (%) of Subjects With Treatment-Emergent Hemophilia Events by Maximum Severity Grade

Body System[b] Event	Maximum Severity Grade[a] Mild	Moderate	Severe	Life-threatening	All
Any event	3 (10.0)	2 (6.7)	0	0	5 (16.7)
Body as a whole					
Back pain	0	1 (3.3)	0	0	1 (3.3)
Cardiovascular system					
Hemorrhage	1 (3.3)	0	0	0	1 (3.3)
Hemic and lymphatic system					
Factor VIII inhibition	2 (6.7)	0	0	0	2 (6.7)
Musculoskeletal system					
Arthralgia	1 (3.3)	1 (3.3)	0	0	2 (6.7)
Joint disorder	1 (3.3)	0	0	0	1 (3.3)

AEs and SAEs are not separated.
c. Only the events with the worst severity are tabulated.
d. Body system totals are not necessarily the sum of the individual events because a subject may report 2 different events in the same body system.

Five (5; 16.7%) subjects reported a total of 7 SAEs during this study. Serious hemophilia events of clinically silent low-titer inhibitors were reported in 2 subjects. Both of these inhibitor events were considered related to ReFacto AF.

No subjects died during this study. There were no clinically significant patterns related to ReFacto AF for blood chemistry or hematology changes during the study. Overall, there was no allergic manifestation to any immune response observed during the study. No physical

findings from routine physical examinations were reported or detected in the analysis of this study. No other observations related to safety were reported or detected in the analysis of this study.

CONCLUSION: The data show that ReFacto AF was safe and efficacious for the perioperative and postsurgical management of subjects with severe and moderately severe hemophilia A undergoing major surgery, regardless of BI or CI administration. Outcomes were favorable with ReFacto AF against a background of multiple major surgical procedures. All efficacy ratings were "excellent" or "good." Intraoperative blood loss was rated as normal in all subjects. In subjects with postoperative blood loss, the blood loss was generally rated as normal. A low frequency of transfusion was reported. AE frequencies were consistent with those expected in the surgical setting. There were no cases of thrombosis. Two clinically silent, positive FVIII inhibitor results were reported; 1 was a low titer persistent inhibitor, the other a transient false positive. The frequency of immune response to ReFacto AF and CHO proteins was low, and there were no allergic reactions.