FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

DATE: May 4, 2011

FROM: Kimberly Lindsey, MD, Medical Officer, Clinical Review Branch, Division of Hematology, OBRR

SUBJECT: STN 125248.254 recombinant human thrombin (RECOTHROM) Post Marketing Study Final Report (Pediatric study to meet PREA requirements) clinical review memo

SUBMISSION DATE: July 12, 2010

DUE DATE: July 11, 2011

SPONSOR: Zymogenetics, Inc.

TO: Nisha Jain, MD, Acting Chief, Clinical Review Branch

Background: This is memo covers the postmarketing study final report for a pediatric study commitment for RECOTHROM.

As part of the approval for RECOTHROM, Zymogenetics requested a pediatric deferral. The sponsor conducted a pediatric trial entitled, "A Phase 4, Open Label, Single Group Safety and Immunogenicity Study of RECOTHROM (rThrombin) in Pediatric Subjects Undergoing Synchronous Burn Wound Excision and Skin Grafting," to fullfil this post marketing commitment. Zymogenetics has now completed this pediatric trial.

RECOTHROM received US approval on January 17, 2008. RECOTHROM is indicated as an adjunct to hemostasis when control of bleeding by conventional surgical techniques (including suture, ligature, and cautery) is ineffective, insufficient, or impractical.

The original protocol and an amendment were submitted to IND 11358 on June 26, 2008 and December 4, 2009. According to the post marketing pediatric deferral under PREA (the Pediatric Research Equity Act), this study was to be completed by December 2010.

Review recommendation:
Sponsor fulfilled pediatric post marketing study requirement. No safety issues identified in this study. The cover letter of the submission does not indicate that the Sponsor wants to seek a pediatric indication or update the pediatric usage section of the package insert.

Study 499H01 synopsis:

Title of Study: A Phase 4, Open-Label, Single-Group Safety and Immunogenicity Study of RECOTHROM®
(rThrombin) in Pediatric Subjects Undergoing Synchronous Burn Wound Excision and Skin Grafting

Date of Report: 25 June 2010

Study Period
Date first subject enrolled: 4 March 2009
Date last subject enrolled: 29 December 2009

Phase of Development: Phase 4

Investigators and Study Centers:
There were 8 participating sites in the United States. Subjects were treated with study drug at 6 of these sites.

Objectives:
Primary
The primary objective of this study was to evaluate the safety of rThrombin administered as an aid to hemostasis during surgery for burn wound excision and skin grafting in a pediatric population.

Secondary
The secondary objective of this study was to evaluate the immunogenicity of rThrombin in a pediatric population.

Primary Endpoint:
- Incidence and severity of adverse events
- Incidence and grade of selected clinical laboratory abnormalities

Secondary Endpoint:
- Incidence of anti-rThrombin product antibody development at Day 29

Study Design:
This Phase 4, open-label, single-group, multi-site study evaluated the safety and immunogenicity of rThrombin in 30 pediatric subjects. The study population included children newborn to 17 years of age who were undergoing synchronous burn wound

excision and skin grafting and required an aid to hemostasis. Subjects received rThrombin during a single surgical procedure (Day 1) and were evaluated through Day 29 after the surgical procedure.
The safety of rThrombin was evaluated by the incidence and severity of adverse events and the incidence and grade of clinical laboratory abnormalities. Immunogenicity was assessed by measuring the incidence of anti-rThrombin product antibodies. Immunogenicity analyses were performed after subjects completed study participation. Investigators were not aware of subject antibody status at the time of the surgical procedure or follow up.

Product: Recombinant human thrombin, 1000 IU/mL, was applied topically to the graft recipient site.

Number of Subjects:
Thirty subjects were enrolled into the study and treated with rThrombin: 11 subjects 0-2 years old, 8 subjects 3-6 years old, 3 subjects 7-11 years old and 8 subjects 12-17 years old.

Inclusion criteria:

- Newborn through 17 years of age
- At least 1 skin graft recipient site that measured at least 1% of total body surface area (TBSA)
- Total initial burn wounds that were estimated to measure < 40% TBSA
- Bleeding for which treatment with rThrombin was indicated during the surgical procedure
- Negative pregnancy test within 2 days prior to study drug treatment
- LAR signed informed consent
- Signed pediatric assent document

Exclusion criteria:

- Gestational age of < 36 weeks at birth (for infants less than 2 years of age)
- Documented active infection at the graft recipient site. (Note-Subjects with resolved infections at potential graft recipient sites were not excluded)
- Acute inhalation injury
- Autologous skin grafting for ischemic ulcer disease or cutaneous malignancies
- Known antibodies or hypersensitivity to study drug or any of its components, or thrombin preparations, or coagulation factors
- Received whole blood, fresh frozen plasma, cryoprecipitate, or platelets within 24 hours prior to study drug treatment. PRBC transfusions were allowed
- HIV history or other immunodeficiency syndrome or taking immunosuppressive medications or anti-rejection medications
- Medical, social or psychosocial factors that could impact subject safety or compliance
- Breastfeeding or being breastfed
- Experimental agent exposure within 30 days of study enrollment or treatment

Blinding:
None

Prior and concomitant therapy:
Investigators recorded all medications used following informed consent and through the end of study (day 29). Prior medications that were ongoing at time of study enrollment were also recorded.

Rescue Treatment:
If hemostasis was not achieved after study treatment and further hemostatic treatment was necessary, administration of additional study drug or other topical hemostats ("rescue" treatment) was permitted. If rescue treatment was needed, it followed a tiered approach.
Additional rThrombin treatment or surgical hemostatic measures (e.g., suture, cautery, or ligature) were considered first, followed by thrombin-free topical hemostats; finally, alternative thrombin-containing hemostats (bovine- or human plasma-derived products) were administered if needed.

Other topical hemostatic agents:
Thrombin free: CoSeal, Avitene, Surgifoam, Ultrafoam, Instat Bioglue
DuralSeal, Bone Wax

Thrombin containing: Thrombin JMI, FloSeal, CoStasis/ Vitagel, Crosseal, Tisseel, Fibrin sealant produced by the blood bank or in the operating room, Evicel, Evithrom

According to the protocol investigators were to consider use of product containing bovine thrombin or human plasma-derived thrombin only after other rescue alternatives failed.

Statistics:
Safety data were summarized in terms of descriptive statistics. Adverse events were classified according to MedDRA. Severity of clinical adverse events and laboratory data were graded using the National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE), if applicable.
A sample size of approximately 30 subjects was considered sufficient to assess safety and immunogenicity in this population.

Schedule of Study Assessments:

Event	Visit1	Visit 2	Visit 3	Visit 4
	Screening/ baseline	Day 1 (Surgery)	Day 2 (16-48 hours Post surgery)	Day 29 End of Study (Day 26-Day 36)
Informed consent and pediatric assent	X			
Eligibility assessment/	X	X		

Event	Visit1	Visit 2	Visit 3	Visit 4
confirmation				
Medical and surgical history, Baseline conditions	X			
Physical examination, including Vital signs	X		X	X
Hematology[a]	X		X	X
Chemistry[b]	X			X
Coagulation[c]	X		X	X
Immunogenicity[d]	X			X
Documentation of surgical Information		X		
rThrombin administration		X		
Adverse events[e]	X	X	X	X
Concomitant medications[e]	X	X	X	X

[a]Complete blood count (CBC) with differential, platelets, hemoglobin, and hematocrit
b Blood urea nitrogen (BUN) and serum creatinine
c Prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR)
d Anti-rThrombin product antibodies; the investigator could defer or cancel the blood draw in children less than 2 years of age for safety concerns
e Collection of adverse events and concomitant medications ongoing from time of informed consent to Day 29

Adverse event reporting:

- Adverse events included those reported by the subject or determined by the investigator during questioning or evaluation of physical examination and laboratory data.
- Adverse event reports were collected from the time the subject signed informed consent through Day 29.
- Adverse events reported prior to the study surgical procedure (Day 1) were considered baseline medical conditions, unless they worsened following study drug administration.

Immunogenicity testing:

Sequence	Purpose	Description
Assay 1	Screen for binding antibodies	Enzyme-linked immunosorbent assay (ELISA) in which a single capture antigen (rThrombin product) was coated on the plate. A threshold was selected that gave a conservative false positive rate of approximately 5%–10% among samples from healthy donors. Clinical samples with optical density values greater than or equal to the threshold were reported as reactive
Assay 2	Determine antibody titer	Using the parameters established for the screening ELISA, serial dilutions were tested for clinical samples that were reactive in the binding assay. The

		dilution that intercepted the threshold was determined, and titer was reported as -(b)(4)- of that dilution. Samples that were reactive in Assay 1, but fell below the threshold in this assay, were reported as nonreactive
.		
Assay 3	Assess antibody specificity	Confirmatory assay in ----------(b)(4)---------- ---------- ---------- ---------- ---------- ---------- ---------- ---------- ----------

In children less than 2 years of age, the clinical investigator could defer or cancel the immunogenicity blood draw if it was determined that the draw would increase the child's risk of requiring transfusion or pose other safety concerns.

RESULTS:

Demographics

Informed consent was provided by 32 subjects. All subjects providing informed consent were eligible for the study, and 30 subjects received treatment with study drug. Of these 30 subjects, 28 completed the study (93.3%). One subject was lost to follow up between the Day 2 and the Day 29 visits and 1 subject discontinued for other reasons (parent withdrawal of consent).

Of the 30 rThrombin treated subjects, 28 (93%) subjects completed the study.
Twenty seven subjects who received rThrombin and had both baseline and post baseline anti rThrombin product antibody assessments were included in the immunogenicity analysis set.

Subject Disposition (adapted from table provided by sponsor)

	Age Group (years)				
	0-2	3-6	7-11	12-17	Total
Subjects providing Informed consent	12	8	3	9	32
Subjects providing Informed consent but Ineligible	0	0	0	0	0
Subjects Eligible but did not Receive study drug	1	0	0	1	2
Safety analysis set (received Study drug)	11	8	3	8	30

	Age Group (years)				
	0-2	3-6	7-11	12-17	Total
Immunogenicity analysis set[a]	9	8	3	7	27
Completed the study, n(%)	10 (90.9%)	8 (100.0%)	3 (100.0%)	7 (87.5%)	28 (93.3%)
Discontinued the study, n (%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	2 (6.7%)
Lost to follow up	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	1 (3.3%)
Other	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)

[a]Subjects who received study drug and have both baseline and post-baseline anti-rThrombin product antibody assessments

Discontinuations:
Two subjects were deemed eligible for treatment but were not treated: 1 was due to a change in operative plan and 1 listed as "other"

Premature discontinuation and lost to follow up (N= 2) 0-2 yrs N=1
12-17years N=1

Protocol Violations

- There were 25 protocol deviations reported for 22 subjects (22/30 (73.3%).
- One or more deviations were reported for
    - 81.8% of subjects 0 to 2 years of age (n=9/11),
    - 62.5% of subjects 3 to 6 years of age (n=5/8),
    - 100% of subjects 7 to 11 years of age (n=3/3), and
    - 62.5% of subjects 12 to 17 years of age (n=5/8).
- No subjects were removed from the study due to protocol deviations
- Major violation: A 6 year old subject had blood drawn 48 hours prior to parental signing of informed consent.

Summary of surgical procedures:
Flames and scalds were the most common types of burns. Ten subjects had burns due to flames and 10 subjects had burns due to scald injuries.

Prior history of thrombin product exposure
History based on prior surgical procedures was negative for 6 subjects
Unknown for 4 subjects and mixture of unknown and negative for 3 of the subjects who had undergone multiple pre study surgical procedures.

Concomitant medications

Use of thrombin-containing products during additional surgical procedures that occurred during each subject's study participation was also evaluated.

Additional surgical procedures were reported for 6 subjects during this clinical trial. Use of rThrombin product during the additional surgical procedure was reported for 1 of these subjects.

Demographics:

Table 8 Demographics and Subject Characteristics

		Age Group (years)				
		0 - 2 (N=11)	3 - 6 (N=8)	7 - 11 (N=3)	12 - 17 (N=8)	Total (N=30)
Age (years)	n	11	8	3	8	30
	Mean (SD)	1.39 (0.44)	4.85 (1.52)	8.47 (0.76)	15.89 (2.30)	6.89 (6.09)
	Median	1.30	4.35	8.30	16.95	4.35
	Min, Max	0.9, 2.4	3.2, 6.9	7.8, 9.3	12.3, 17.8	0.9, 17.8
Gender, n(%)	Male	5 (45.5%)	4 (50.0%)	3 (100.0%)	6 (75.0%)	18 (60.0%)
	Female	6 (54.5%)	4 (50.0%)	0 (0.0%)	2 (25.0%)	12 (40.0%)
Race, n(%)	American Indian/Alaska Native	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
	Black or African American	2 (18.2%)	3 (37.5%)	0 (0.0%)	1 (12.5%)	6 (20.0%)
	Hispanic	4 (36.4%)	3 (37.5%)	1 (33.3%)	1 (12.5%)	9 (30.0%)
	White	4 (36.4%)	2 (25.0%)	2 (66.7%)	6 (75.0%)	14 (46.7%)
Height (cm)	n	11	8	3	8	30
	Mean (SD)	82.2 (7.6)	111.3 (12.6)	132.8 (3.2)	168.0 (12.2)	117.9 (36.1)
	Median	80.0	113.0	133.0	168.9	113.0
	Min, Max	70, 99	90, 124	130, 136	152, 188	70, 188
Weight (kg)	n	11	8	3	8	30
	Mean (SD)	11.2 (1.4)	19.1 (4.2)	26.2 (3.7)	67.4 (19.2)	29.8 (25.4)
	Median	11.0	17.4	24.6	63.0	17.4
	Min, Max	9, 13	15, 24	24, 31	51, 110	9, 110
TBSA (m^2)[a]	n	11	8	3	8	30
	Mean (SD)	0.51 (0.04)	0.77 (0.12)	0.98 (0.07)	1.77 (0.30)	0.96 (0.54)
	Median	0.50	0.73	0.94	1.72	0.73
	Min, Max	0.5, 0.6	0.6, 0.9	0.9, 1.1	1.5, 2.4	0.5, 2.4

[a] Total Body Surface Area = square root of [Ht (cm) * Wt (kg) divided by 3600]

- Mean (standard deviation [SD]) subject age was 6.89 years (6.09) and subjects ranged from 0.9 to 17.8 years of age
- 11 subjects were 0 to 2 years of age (mean=1.39 years), 8 subjects were 3 to 6 years of age (mean=4.85 years), 3 subjects were 7 to 11 years of age (mean=8.47 years), and 8 subjects were 12 to 17 years of age (mean=15.89 years)
- 12 female subjects (n=12/30; 40.0%)
- 18 male subjects (n=18/30; 60.0%)
- Approximately half of the subjects within the youngest age categories (0 to 2 years of age and 3 to 6 years of age) were female

- Subjects in the 2 oldest age categories (7 to 11 years of age and 12 to 17 years of age) were predominantly male

According to the sponsor the gender distributions are comparable to those reported by the American Burn Association for patients admitted to burn centers from 2000-2009

- Median TBSA was 0.73 m^2 for the total subject population
- Median TBSA increased with age

Sponsor's burn surgery summary table 10. Reviewer agrees with summary table.

Table 10 Burn Surgery Summary

		Age Group (years)				
		0 - 2 (N=11)	3 - 6 (N=8)	7 - 11 (N=3)	12 - 17 (N=8)	Total (N=30)
Indication, n(%)	Primary Skin Graft	11 (100.0%)	8 (100.0%)	3 (100.0%)	8 (100.0%)	30 (100.0%)
Burn Type, n(%)	Flame	0 (0.0%)	3 (37.5%)	2 (66.7%)	5 (62.5%)	10 (33.3%)
	Scald	6 (54.5%)	3 (37.5%)	0 (0.0%)	1 (12.5%)	10 (33.3%)
	Thermal	5 (45.5%)	1 (12.5%)	1 (33.3%)	0 (0.0%)	7 (23.3%)
	Other	0 (0.0%)	1 (12.5%)	0 (0.0%)	2 (25.0%)	3 (10.0%)
Graft Type, n(%)	Mesh Graft	1 (9.1%)	1 (12.5%)	1 (33.3%)	4 (50.0%)	7 (23.3%)
	Sheet Graft	10 (90.9%)	7 (87.5%)	2 (66.7%)	4 (50.0%)	23 (76.7%)
% TBSA[a] Burned	n	11	8	3	8	30
	Mean (SD)	5.86 (5.41)	8.00 (5.88)	3.17 (1.26)	3.69 (2.90)	5.58 (4.88)
	Median	4.00	7.00	3.00	2.75	4.00
	Min, Max	1.0, 20.0	2.0, 18.0	2.0, 4.5	1.5, 10.5	1.0, 20.0
% TBSA[a] Grafted	n	11	8	3	8	30
	Mean (SD)	2.45 (1.51)	6.13 (6.53)	2.83 (1.76)	2.88 (3.15)	3.58 (4.02)
	Median	2.00	3.50	3.00	2.00	2.00
	Min, Max	1.0, 5.0	1.5, 18.0	1.0, 4.5	1.0, 10.5	1.0, 18.0
Additional/ Rescue Treatment[b], n(%)		11 (100.0%)	8 (100.0%)	3 (100.0%)	8 (100.0%)	30 (100.0%)

[a] Total Body Surface Area
[b] Subjects receiving additional hemostatic measure and/or rescue treatment during study surgery

- The mean (SD) percentage of TBSA burned was 5.58% (4.88).

Additional hemostatic treatments:

- All subjects (n=30/30; 100%) required additional hemostatic treatment or rescue hemostatic measures during the study surgical procedure
- The most commonly used additional treatments were epinephrine, which was used for all subjects (n=30/30; 100%), and cautery, which was used for 53.3% subjects (n=16/30
- Clysis, tourniquets, pressure, suture, and pressure with epinephrine soaks were also used

Extent of Exposure

- Estimated median volume of study drug administered per subject during the surgical procedure was 8.0 mL, with a range of 1 mL to 36 mL
- Median volume of study drug administered was larger for older subjects (12.0 mL for subjects 7 to 11 years of age and 11.0 mL for subjects 12 to 17 years of age) than for younger subjects (7.0 mL for subjects 0 to 2 years of age and 6.5 mL for subjects 3 to 6 years of age
- The maximal volume of study drug administered was 36 mL, administered to 1 subject who was 3 to 6 years of age. Study drug administration was 20 mL or less for the other 29 subjects
- Recombinant thrombin was most commonly applied to extremities.
- Application of rThrombin to areas of the body other than the extremities was more common for younger subjects than for older subjects; 9 of the 11 subjects with a skin graft located on an area of the body other than the extremities were in the 2 younger age groups (0 to 2 years of age or 3 to 6 years of age).

Safety

No deaths occurred during the study. One subject (n=1/30; 3.3%) experienced protocol defined treatment-emergent serious adverse events. This subject experienced 2 events (skin graft infection and skin graft failure).

Treatment emergent adverse events reported for ≥10% of subjects

Anemia was more commonly reported for the youngest age group (63.6% of subjects 0 to 2 years of age) than for subjects in the 3 older age groups (0% to 12.5% of subjects in these age groups). This finding is not surprising given that anemia is a common consequence of blood loss during the graft procedure, particularly in infants and toddlers, who have lower iron reserves compared to other age groups.

Hypersensitivity reactions:

Coagulation studies:

Immunogenicity:

Immunogenicity (i.e. anti-rThrombin product antibodies) was evaluated on samples that were obtained at baseline and Day 29. The analyses were conducted after each subject's study participation concluded for all subjects who received at least 1 application of rThrombin study drug during the surgical procedure and had data from baseline and post baseline.

The following table, reported by the sponsor, summarizes the immunogenicity evaluation of the subjects. (Table 14 Antibody Status by Visit):

		Age group (years)				
		0-2	3-6	7-11	12-17	Total
	rThrombin Antibody	(N=9)	(N=8)	(N=3)	(N=7)	(N=27)
Visit	Status	N(%)	N(%)	N(%)	N(%)	N(%)
Baseline	Pre-exisiting [a]	1 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.7%)
Day 29	Antibody Positive [a,b]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	95% CI (%,%) [c]	(0.0, 33.6)	(0.0, 36.9)	(0.0, 70.8)	(0.0, 41.0)	(0.0, 12.8)
	Seroconversion [d]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	≥ 1.0 Titer Change [e]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

[a] Denominator includes subjects in the immunogenicity dataset
[b] Subjects are considered antibody positive if they seroconvert or have a post-baseline increase of >= 1.0 titer unit in anti-rThrombin product antibody titer
[c] 95% exact confidence interval
[d] Denominator includes subjects who did not have pre-existing anti-rThrombin product antibodies at baseline and who had post-baseline immunogenicity data
[e] Denominator includes subjects who had pre-existing anti-rThrombin product antibodies at baseline and who had post-baseline immunogenicity data

The immunogenicity analysis set included the 27 subjects who received study drug and had both baseline and post-baseline anti-rThrombin product antibody assessments. No subjects became antibody-positive for anti-rThrombin product antibodies at Day 29 (0 of 27 subjects; 0%; 95% CI: 0.0%, 12.8%). One subject had pre-existing anti-rThrombin antibodies at baseline, but antibody titer did not increase ≥1.0 unit (≥10-fold) at Day 29.

Conclusions/Comments:
No safety concerns in pediatric population identified in this post marketing study.