

Chairman's Summary - RECOTHROM

MEMORANDUM

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

Date: January 11, 2008

To: Mark Shields, HFM 380 and the File of STN 125248

From: Roman Drews, HFM-392

Through:

Timothy Lee, HFM-392

Acting Chief, Laboratory of Hemostasis, DH, OBRR

Subject: Chairman's Summary for the Approval of an Original Biologics License Application from ZymoGenetics, Inc. for Thrombin topical (Recombinant) [RECOTHROM®]

This biologics license application was reviewed by a committee that included the following CBER reviewers: Dr. Paul Aebersold (Clinical), Dr. Paul Buehler

(Pharmacology/Toxicology), Mr. Sean Byrd (Facility inspector), Dr. Roman Drews (CMC/Chairperson), Ms. Maryann Gallagher (Advertising and Labeling), Mr. Myke Hall (Electronic integrity), Dr. Paul Hsieh (Biostatistics), Dr. Nisha Jain (Clinical), Dr. Nancy Kirschbaum (CMC), Ms. Eleanor Koo (CMC), Dr. Timothy Lee (CMC consult), Dr. Kimberly Lindsey (Clinical), Ms. Carolyn Renshaw (Facility consult), Mr. Mark Shields (Administrative/Regulatory), Ms. Nancy Waites (CMC/Facility), and Ms. Janet White (Bioresearch monitoring). Based on the data submitted by ZymoGenetics, the review committee found the safety, potency, and efficacy of RECOTHROM to be acceptable and recommends approval of the BLA STN 125248.

Proprietary name

The proprietary name, RECOTHROM, was approved by OCBQ/DCM/APLB. Pursuant to 21 CFR 201.6(a), the name RECOTHROM is not false or misleading; pursuant to 21 CFR 201.10(c)(3), it is not fanciful; pursuant to 21 CFR 201.10(c)(5), the name is sufficiently different in spelling or pronunciation to mitigate concern regarding confusion with another marketed product.

Biological Product Name

Thrombin topical (Recombinant)

Full Prescription Information (FPI)

A copy of the approved FPI is included as Appendix I

Indication for use

RECOTHROMT Thrombin topical (Recombinant) is indicated as an aid to hemostasis whenever oozing blood and minor bleeding from capillaries and small venules is accessible and control of bleeding by standard surgical techniques is ineffective or impractical. RECOTHROMT may be used in conjunction with an absorbable gelatin sponge, USP.

Dosage form

The RECOTHROMT product is supplied in a kit containing a vial of RECOTHROMT lyophilized powder, a pre-filled diluent syringe, and accessories for needle-free reconstitution.

Route of administration and recommended dosage

- Do not inject directly into the circulatory system.
- Do not use for the treatment of massive or brisk arterial bleeding.

When reconstituted with 5 mL of sterile 0.9% sodium chloride injection, USP, as directed, the solution contains approximately 1000 IU/mL of rthrombin. The prepared solution is then applied directly to the bleeding site or in conjunction with an absorbable gelatin sponge, USP.

Reconstituted solutions of RECOTHROMT prepared with sterile 0.9% sodium chloride injection, USP, can be stored for up to 24 hours at 2 °C to 25 °C (36 °F to 77 °F). The reconstituted solution should be discarded after 24 hours.

RECOTHROMT is manufactured via recombinant DNA technology from a genetically modified CHO cell line. The cell culture process employs no additives of human or animal origin. RECOTHROMT is identical in amino acid sequence and structurally similar to plasma-derived human thrombin. Also, it has hemostatic activities comparable to human thrombin. The manufacturing process operates consistently within established operational ranges producing product that meets release acceptance criteria.

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Manufacture of Drug Product

The commercial manufacturing process for the 5000-IU RECOTHROMT drug product consists of ----- bulk drug substance, compounding, aseptic filling, lyophilization, and finishing. Released finished product vials are then labeled and packaged. The drug product is packaged into a commercial kit packaged in a partitioned white paperboard box. The 5000-IU commercial product kit includes the following components:

- A vial of RECOTHROMT containing 5000 IU of rthrombin
- A Becton, Dickinson and Company (BD) PosiFlushT pre-filled normal saline flush syringe containing 5 mL of sterile 0.9% sodium chloride injection, USP
- An Alaris SmartSite® needle-free transfer device
- A BD 5-mL Luer-LokT tip sterile empty syringe
- A RECOTHROMT package insert

Final Container testing

Final product release tests are performed on every lot of RECOTHROMT. In addition to required tests for Sterility (21 CFR §610.12), the following tests are performed: appearance, thrombin potency, thrombin content, product and process related impurities, and excipients.

Stability

The RECOTHROMT drug product is stable for 24 months when stored at 2 °C to 25 °C. Reconstituted solutions of RECOTHROMT prepared with sterile 0.9% sodium chloride injection, USP, may be stored for up to 24 hours at 2 °C to 25 °C (36 °F to 77 °F).

Validation

Utility systems, manufacturing equipment, manufacturing processes, and analytical methods used in the production of RECOTHROMT have been validated according to established protocols. Procedures are in place to ensure routine maintenance of equipment and specified monitoring of environmental conditions and quality oversight within the production and testing facilities.

The master cell bank and the working cell bank were characterized, stable in genotype, and free of any detectable bacterial or fungal contamination. No adventitious virus was detected

in a conventional testing program. The manufacturing processes for RECOTHROMT were validated for consistency, robustness, and for removal of impurities. Assays used for testing and release of the drug substance and drug product were validated for accuracy, precision, and reproducibility. Samples from three qualification lots were submitted to CBER for testing and met specific lot release testing requirements.

Establishment

A pre-license establishment inspection of the -----
----- was conducted on 14-18 May 2007. A pre-approval
inspection of the -----
was waived. A pre-license inspection of the ZymoGenetics testing facility was conducted on 16-20 July 2007. An FDA Form 483 was issued at each location for each inspection; the companies responded to all observations and their corrective actions were found to be adequate and complete. Both establishments were found to be in compliance with current good manufacturing practice standards. A copy of the inspection reports, the inspectional closeout memoranda, and the inspection waiver for the ----- facility are on file.

Environmental Assessment

ZymoGenetics, Inc., was granted a categorical exclusion from an environmental assessment under 21 CFR 25.31(c).

Pharmacology and Toxicology

The safety, toxicity, efficacy, absorption, distribution, inhibitor binding, and clearance of RECOTHROMT have been evaluated in animals.

Thrombin directly promotes coagulation through the activation of platelets and the formation of stably cross-linked fibrin clots. The ability of thrombin to bypass the initial enzymatic steps of the coagulation cascade provides a clear rationale for its use as a topical hemostatic agent.

Pharmacology and Pharmacokinetics

Pharmacology and pharmacokinetic studies were designed to show that RECOTHROMT has coagulation-related biology similar to human plasma thrombin when applied to a site of bleeding. Several nonclinical studies showed the following:

- RECOTHROMT was able to significantly reduce local bleeding (as measured by time to hemostasis, TTH) in 2 relevant models of bleeding (rat and rabbit) when applied with a gauze pad or gelatin sponge. Dose-response studies demonstrated that RECOTHROMT reduced TTH with statistical significance at strengths greater than 500 U/mL; 1000 U/mL was selected as the strength for Phase 2 and Phase 3 studies to achieve maximum reduction of bleeding in a wide variety of settings. (Note that nonclinical study doses were expressed at the time in US units [U] rather than International units [IU]).
- Data from a porcine split-thickness excisional wound model demonstrated that RECOTHROMT is an effective hemostatic agent in the absence of a carrier matrix or "passive hemostat" (e.g., gauze or gelatin sponge); spray application of rthrombin reduced TTH significantly as compared to saline control (or no treatment).
- RECOTHROMT binds to endogenous inhibitors and these rthrombin-inhibitor complexes are cleared via the liver as determined by a biodistribution study in nonhuman primates (using radiolabeled rthrombin). The initial half-life was estimated at approximately 0.17 hours, suggesting the rapid formation of rthrombin-inhibitor complexes. This is consistent with the fate of endogenous plasma thrombin.

- PAR1 and PAR4 receptors were cleaved by rthrombin. The rthrombin induced platelet aggregation and factor XIII activation and was able to convert autologous fibrinogen to fibrin. These activities are central to the ability of RECOTHROMT to facilitate local hemostasis and are consistent with the activities of human plasma thrombin.
- RECOTHROMT induced clot formation in plasma isolated from humans, nonhuman primates, and rabbits.

Toxicology

Nonclinical toxicology studies demonstrated that RECOTHROMT was safe and well tolerated in rabbits and nonhuman primates. RECOTHROMT toxicology studies were not influenced by neutralizing antibody responses in rabbits or non-human primates. Specific nonclinical studies to evaluate RECOTHROMT safety demonstrated the following:

- No signs of irritation or cytotoxicity were observed when RECOTHROMT (1000 U/mL) was applied to normal or abraded skin or when instilled into the eyes of rabbits (GLP).
- No evidence of toxicity or altered wound healing was observed when RECOTHROMT (1000 U/mL) was applied via a gelatin sponge to a surgically induced template liver wound in nonhuman primates (GLP). Specific evaluation of plasma coagulation, hematology, clinical chemistry, and microscopic pathology revealed no evidence of local or systemic toxicity. One animal had a single positive anti rthrombin antibody titer to RECOTHROMT (1 out of 4 time points evaluated).
- No signs of local or systemic toxicity were observed when RECOTHROMT was administered to nonhuman primates once weekly subcutaneously for 4 weeks (GLP). No antibody formation to RECOTHROMT was observed.

Overall, these studies demonstrate that RECOTHROMT has similar coagulation-related biology to human plasma thrombin and is well tolerated, nontoxic, and minimally immunogenic in animal models.

Clinical

A Phase 3 randomized, double blind, controlled study of RECOTHROMT vs. bovine thrombin (Thrombin-JMI) for surgical hemostasis was performed. The primary objective of the study was to evaluate the relative efficacy of RECOTHROMT vs. Thrombin-JMI, and the secondary objectives were to evaluate safety and immunogenicity. Eligible patients were ≥18 years of age, undergoing liver resection, spine, peripheral arterial bypass, or arterial-venous graft access surgery. The exclusion criteria included history of hypersensitivity to bovine thrombin components, bovine materials, or porcine collagen; receipt of blood products within 24 hours prior to surgery; surgery within the last 30 days; or a history of heparin-induced thrombocytopenia. Eligible patients were randomly assigned in a 1:1 ratio to receive RECOTHROMT (1000 IU/mL) or Thrombin-JMI (1000 IU/mL). Blinded study drug was topically applied with an absorbable gelatin sponge and time to hemostasis (TTH) was assessed for up to 10 minutes. The primary efficacy endpoint was TTH, summarized as the incidence of hemostasis within 10 minutes. The primary efficacy analysis included all patients who received blinded study drug at one of 4 pre-specified bleeding site types (epidural venous plexus, hepatic resection site, PAB proximal anastomosis, or AV graft arterial anastomosis). Bleeding appropriate for evaluation was defined as mild to moderate in intensity, either on its own or remaining after brisk bleeding had been controlled by standard surgical modalities. Exclusion of a >15% difference in incidence rates was indicated by the lower limit of a 95% confidence interval adjusted for interim analyses. Safety was assessed for 1 month following surgery and included adverse events, clinical

laboratory results, and immunogenicity testing. Immunogenicity was evaluated using sequential enzyme linked immunosorbent assays (ELISA) to screen for anti-product antibodies, determine antibody titers, and assess antibody specificity. Blood samples were collected at baseline and at day 29 for 97% of the subjects in both treatment groups. For subjects randomized to RECOTHROMT, the samples were analyzed by ELISA for antibodies to rthrombin, Chinese hamster ovary (CHO) host cell protein, and pro-thrombin activator (used in the conversion of single chain precursor to active RECOTHROMT). For subjects randomized to bovine thrombin, the samples were analyzed by ELISA for antibodies to bovine thrombin product. Anti-product antibody development was defined as either seroconversion or a ≥ 1.0 titer unit increase (≥ 10 fold) in anti-product antibody titer following study treatment. Fisher's exact test was used to compare the incidence of anti-product antibodies between treatment groups.

Clinical Pharmacology

Thrombin activates platelets and cleaves fibrinogen to fibrin, leading directly to clot formation. Thrombin also activates FXIII, leading to fibrin cross-linking and clot stability. The ability of thrombin to bypass the initial enzymatic steps of the coagulation pathway provides a clear rationale for the use of RECOTHROMT as a topical hemostatic agent. Thrombin is rapidly neutralized by naturally circulating plasma inhibitors, including antithrombin III, alpha-2-macroglobulin, and heparin cofactor II, which act to limit its duration of action and prevent the active form from diffusing into the general circulation.

As shown in nonclinical studies, RECOTHROMT applied topically to sites of bleeding does not circulate in the blood as a free, active molecule, but is rapidly bound to endogenous inhibitors and cleared via the liver. Due to the limited bioavailability of active rthrombin, no systemic exposure-related effects on safety or efficacy are anticipated. The strength (nominally 1000 IU/mL) and formulation used during clinical studies are identical to the formulation to be marketed.

Clinical pharmacokinetic studies were not conducted, as RECOTHROMT acts locally, does not appreciably enter the circulation when applied topically, and is rapidly bound to endogenous inhibitors upon entry into the circulation.

Efficacy

In the Phase 3 study, the incidence of hemostasis within 10 minutes was 95.4% for subjects in the RECOTHROMT group and 95.1% for subjects in the active control group. This represents a 0.3% (95% CI, -3.7% to 4.4%) difference in subjects receiving RECOTHROMT compared to those receiving Thrombin-JMI, establishing that the 2 treatments have comparable efficacy based upon the predefined margin of 15% (Table 1). The overall incidence of hemostasis within 10 minutes in subjects randomized to RECOTHROMT in Phase 2 was 90% (epidural venous plexus, 86%; hepatic resection site, 100%; PAB, 83%; and AV graft, 94%).

Table 1. Incidence of hemostasis within 10 minutes in Phase 3

| | RECOTHROM™ | | Thrombin-JMI | | Treatment Effect ¹ |
|------------------------|------------|--------------|--------------|--------------|-------------------------------|
| Bleeding Site Type | N | % hemostasis | N | % hemostasis | % (95% CI) |
| Overall | 198 | 95.4 | 203 | 95.1 | 0.3 (-3.73, 4.35) |
| Epidural venous plexus | 61 | 98.4 | 61 | 98.4 | 0.0 (-4.51, 4.51) |
| Hepatic resection site | 62 | 98.4 | 63 | 96.8 | 1.6 (-3.78, 6.91) |
| PAB proximal | 40 | 85.0 | 42 | 85.7 | -0.7 (-16.0, 14.6) |

| | RECOTHROM™ | | Thrombin-JMI | | Treatment Effect ¹ |
|--------------------|------------|--------------|--------------|--------------|-------------------------------|
| Bleeding Site Type | N | % hemostasis | N | % hemostasis | % (95% CI) |
| AV graft arterial | 35 | 97.1 | 37 | 97.3 | -0.2 (-7.75, 7.45) |

Treatment effect = RECOTHROM - bovine Thrombin

In Phase 3, both treatments achieved similar efficacy among surgery types (Table 1). Differences between treatment groups (RECOTHROMT - Thrombin-JMI) in incidence of hemostasis within 10 minutes ranged from -0.7% (95% CI -16.0% to 14.6%) in PAB surgery to 1.6% (95% CI -3.8% to 6.9%) in hepatic surgery. Consistent with the Phase 2 estimates, the incidence of hemostasis in subjects undergoing PAB was lower than the other 3 surgery types. This may be a consequence of the high percentage (86% in Phase 3) of anticoagulant or anti-platelet medication usage in this group relative to subjects undergoing other types of surgery (2% to 38%), and the high-pressure blood flow at the PAB anastomotic sites.

The percentage of subjects achieving hemostasis at 1.5, 3, 6, and 10 minutes is listed in Table 2.

Table 2 . Cumulative Incidence of Hemostasis Over Time ^{1, 2}

| ¹ Time (Minutes) | ² RECOTHROM™ (N=198) n (%) | Thrombin-JMI (N=203) n (%) |
|-----------------------------|---|----------------------------------|
| 1.5 | 95 (48%) | 93 (46%) |
| 3 | 160 (81%) | 146 (72%) |
| 6 | 183 (92%) | 178 (88%) |
| 10 | 189 (95%) | 193 (95%) |

¹ Includes 401 efficacy evaluable subjects.

² Percentages are rounded to whole numbers.

Minor differences in health outcomes through day 29 including duration of surgical procedure, length of hospital stay, use of alternative topical hemostatic agents at TTH evaluation sites, use of blood products including red blood cells, and re-operation did not raise concerns.

Safety

RECOTHROMT used in conjunction with an absorbable gelatin sponge and no specific adverse events were established as adverse reactions causally related to RECOTHROMT administration. Among the 411 subjects treated with study drug in the Phase 3 study, all but 2 subjects (1 subject/treatment group) reported adverse events.¹ Most events were moderate in severity and had a similar incidence in the RECOTHROMT and Thrombin-JMI treatment groups. The most common adverse events were incision site complication (63% for both treatment groups), procedural pain (RECOTHROMT 29%; Thrombin JMI 34%), and nausea (RECOTHROMT 28%; Thrombin-JMI 35%). Serious adverse events were reported by 18% of subjects treated with RECOTHROMT and 22% with Thrombin-JMI. Overall, similar rates of adverse events, serious adverse events, and deaths were observed in Phase 3 and Phase 2 studies.

Adverse events of interest were pre-specified, based on the thrombin mechanism of action, use of absorbable gelatin sponge, USP, historical reporting in association with cross-reacting antibodies to bovine thrombin product, and results from RECOTHROMT Phase 2 clinical trials. The incidences of these pre-specified events were similar between treatment groups (see Table 3).

Table 3. Events of Interest in the RECOTHROMT Phase 3 Study

| AE Category ¹ | RECOTHROM TM (N=205) n (%) | Thrombin-JMI (N=206) n (%) |
|---|--|---|
| Subjects with any event category | 124 (60%) | 136 (66%) |
| Bleeding | 27 (13%) | 24 (12%) |
| Cardiac | 41 (20%) | 38 (18%) |
| Hypersensitivity | 30 (15%) | 37 (18%) |
| Nausea + vomiting | 68 (33%) | 83 (40%) |
| Other infection | 26 (13%) | 31 (15%) |
| Post-operative wound infection | 19 (9%) | 22 (11%) |
| Thromboembolic | 12 (6%) | 10 (5%) |
| ¹ Adverse events were included in event categories based on a blinded review of the investigator verbatim and coded terms. | | |

Laboratory abnormalities were consistent with surgical procedure, pathologic state, and co-morbidities and were not considered causally related to either product.

Immunogenicity

The development of anti-product antibodies, a pre-specified study endpoint, was monitored in the Phase 3 clinical trial.¹ Blood samples were collected at baseline and at day 29 for 97% of the subjects in both treatment groups. For subjects randomized to Thrombin, topical (Recombinant), the samples were analyzed by ELISA for antibodies to RECOTHROMT, Chinese hamster ovary (CHO) host cell protein, and pro-thrombin activator (used in the conversion of single chain precursor to active RECOTHROMT). For subjects randomized to bovine thrombin, the samples were analyzed by ELISA for antibodies to bovine thrombin product.

Treatment with RECOTHROMT resulted in a statistically significantly lower incidence of specific anti-product antibody development. Three of 198 (1.5%, 95% CI; 0 to 4%) of the patients in the RECOTHROMT arm developed specific anti-thrombin product antibodies (1 patient also developed anti-CHO host cell protein antibodies). No subjects developed antibodies to pro-thrombin activator. Forty-three of 200 subjects (22%, 95% CI; 16 to 28%) in the bovine thrombin arm developed specific antibodies to bovine thrombin product. None of the antibodies in the RECOTHROMT group neutralized native human thrombin.

Antibodies against bovine thrombin product were not tested for neutralization of native human thrombin. Development of antibodies in **either** group did not lead to any adverse events such as excessive bleeding.

At baseline in the Phase 3 study, 1.5% of subjects (n=3/198) in the RECOTHROMT group had positive anti-thrombin product antibody titers compared with 5% of patients in the bovine thrombin product group (n=10/200). Of the patients who had detectable anti-product

antibodies at baseline, 0 of 3 in the RECOTHROMT group and 8 of 10 in the bovine thrombin group exhibited ≥ 1.0 titer unit (≥ 10 fold) increase in antibody levels after study treatment.

In Phase 2 studies, incidence of antibody development following treatment with RECOTHROMT was 1.2% (95% CI, 0% to 6.5%) compared to 2.4% (95% CI, 0.1% to 12.9%) for placebo.

The detection of antibody formation is highly dependent upon the sensitivity and specificity of the assay. The absolute immunogenicity rates reported here are difficult to compare with results from studies of other products due to differences in assay methodology, patient populations, and other underlying factors. Limited data (n=6) are currently available on repeat exposure to RECOTHROMT.

Pediatric Research Equity Act (PREA)

RECOTHROMT has not been studied in pediatric patients; ZymoGenetics has been granted a deferral of pediatric studies for all age groups until the submission of the protocol in June 2008 and final study report in December of 2010.

Post-Marketing Studies and Commitments

Clinical Post-Marketing Commitment

1. Deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of these postmarketing studies shall be reported annually according to 21 CFR 601.70. These commitments are listed below.
 - a. Deferred pediatric study under PREA as an aid to hemostasis whenever oozing blood and minor bleeding from capillaries and small venules is accessible and control of bleeding by standard surgical techniques is ineffective or impractical in all age groups.
 - b. Study Protocol by: June 2008
 - c. Final Report Submission by: December 2010
2. ZymoGenetics will conduct a postmarketing study to evaluate immunogenicity and safety of re-exposure to RECOTHROMT. The final clinical study protocol will be submitted 90 days following approval, with first patient first visit (FPFV) approximately 6 months following approval of the protocol and last patient last visit up to 25 months after FPFV.

Chemistry, Manufacturing, Controls Post-Marketing Commitments

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Regarding Stability,

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References:

1. Chapman WC, Singla N, Genyk Y, McNeil JW, Renkens Jr KL, Reynolds TC, Murphy A, Weaver FA. A Phase 3, Randomized, Double-Blind Comparative Study of the Efficacy and Safety of Topical Recombinant Human Thrombin and Bovine Thrombin in Surgical Hemostasis. J Am Coll Surg 2007;205:256-265