European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

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WITHDRAWAL ASSESSMENT REPORT FOR

RECOTHROM
(thrombin alpha)

EMEA/H/C/1063

Day 180 Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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LIST OF ABBREVIATIONS

2M alfa-2-macroglobulin
AE adverse event
aPTT activated partial thromboplastin time
ATIII anti-thrombin III
AV arteriovenous
bThrombin, bT bovine thrombin (Thrombin-JMI)
CFR Code of Federal Regulations
CHO (HCP) Chinese hamster ovary (host cell protein)
CI confidence interval
CPMP Committee for Proprietary Medicinal Products
CSR clinical study report
eCTD electronic Common Technical Document
EHS event of heightened surveillance
FDA Food and Drug Administration
FXIII Factor XIII
GCP Good Clinical Practice
ICH International Conference on Harmonisation
IDMC independent data monitoring committee
IND investigational new drug
INR international normalized ratio
ISO International Standards Organization
IU International Unit
IVRS interactive voice response system
MedDRA Medical Dictionary for Regulatory Activities
mL milliliter
N/A not applicable
NDA New Drug Application
PAB peripheral arterial bypass
PT prothrombin time
PTA prothrombin activator
rh Thrombin recombinant human thrombin - INN: thrombin alfa
SAE serious adverse event
SCI Statistics Collaborative, Inc
SPA special protocol assessment
TTH time to haemostasis

I. RECOMMENDATION

Based on the review of the data on quality, pre-clinical and clinical safety and efficacy:

The application for Recothrom, in the indication of "supportive treatment in surgery for improvement of haemostasis where standard surgical techniques are insufficient", is not approvable since "major objections" remain which preclude a recommendation for marketing authorisation.

II. EXECUTIVE SUMMARY

II.1 About the product

Product
This is a first centralised application for a thrombin manufactured using recombinant DNA techniques. Thrombin alfa is to be used with an absorbable gelatin sponge, which is co-packed in the Recothrom 5,000 IU final product pack. The Applicant intends to provide also a 20,000 IU product pack which will contain a spray applicator kit instead of the gelatin sponge. This is suggested to be used in cases where the use of sponges is not possible or impractical.

Mode of action
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 thrombin alfa as a topical haemostatic agent.

Pharmacological classification
B02BC06 Group: Antihaemorrhagics/Local haemostatics

Claimed indication:
Supportive treatment in surgery for improvement of haemostasis where standard surgical techniques are insufficient.

II.2 The development programme/Compliance with CHMP Guidance/Scientific Advice

Results of 8 clinical studies have been provided to support the claimed indication

Phase	Study No	Subject Population	Primary Objective	Treatments Studied [Application mode]	Thrombin alfa N[a] /n[b] (n[c])	Total N[d]
I	499C05 Part I	Spinal surgery	Evaluate the safety of thrombin alfa	thrombin alfa (3 concentrations) [gelatin sponge]	9 / N/A(N/A)	9
II	499C05 Part II	Spinal surgery	Evaluate the safety of thrombin alfa	thrombin alfa; placebo [gelatin sponge]	33 / 21 (12)	42
	499C06	Hepatic resection	Evaluate the safety of thrombin alfa	thrombin alfa; placebo [gelatin sponge]	17 / 14 (3)	28
	499C07	PAB surgery	Evaluate the safety of thrombin alfa	thrombin alfa; placebo [gelatin sponge]	17 / 12 (5)	27
	499C08	AV graft formation for hemodialysis access	Evaluate the safety of thrombin alfa	thrombin alfa; placebo [gelatin sponge]	21 / 17 (4)	33
	499E02	Autologous skin grafting following burn injury	Evaluate the safety of thrombin alfa	thrombin alfa [Spray applicator]	72 / N/A(N/A)	72
				Phase I/II total:	169	211
III	499E01	Multisurgery[e]	Relative efficacy of thrombin alfa to active comparator	thrombin alfa; bThrombin [gelatin sponge]	205 / N/A(N/A)	411
				Program total[f]	374	622

a Total exposed to thrombin alfa
b Subjects who received thrombin alfa as double-blind treatment
c Subjects allocated to placebo treatment who received thrombin alfa as rescue treatment after initial double-blind treatment
d Total studied in all treatment arms
e Spinal surgery, hepatic resection, 2 vascular surgeries (PAB surgery, and AV graft formation)
f Total of thrombin alfa treated subjects
Abbreviations: AV = arteriovenous; N/A = not applicable; PAB = peripheral arterial bypass

With the responses to Day 120 List of Questions, the Applicant submitted a further study report on 'A Phase IIIb, open-label, single-group immunogenicity and safety study of topical recombinant thrombin (rThrombin) in surgical hemostasis' (Study No. 499F04):

Study population: spinal or vascular surgery. Patients had a history of prior surgery with a high likelihood of bovine thrombin exposure within previous 3 years (n=209).

Primary objective: immunogenicity (to compare the development of anti-rThrombin product antibodies at Day 29 between subjects with and without baseline anti-bovine thrombin product antibodies).

Treatments studied: thrombin alfa in combination with absorbable gelatine sponge or powder.

A CPMP Guideline on the clinical investigation of plasma derived fibrin sealant/haemostatic products (CPMP/BPWG/1089/00) was in force since 29 July 2004 and is relevant to the clinical assessment of Thrombin intended for topical use. The latter guidance was instituted for plasma derived products containing not just thrombin but also other additional coagulation factors. Core SmPC for plasma derived fibrin sealant/haemostatic products (CPMP/BPWG/153/00) outlines the Core SmPC requirements for topical haemostatic products. CPMP/EWP/2330/99 guidance for the application comprising one pivotal phase III study is also relevant to this application.

The study results as well as the quality and pre-clinical data were discussed during scientific advice meetings with the national authorities of UK, France, Germany and Spain as well as with Canada. Overall, the applicant complied with national advice.

II.3 General comments on compliance with GMP, GLP, GCP

GLP
The pivotal safety studies were conducted in compliance with the GLP regulations.

GCP
All studies were conducted in the USA in accordance with Good Clinical Practice (GCP) regulations and guidelines (21 CFR Parts 11, 50, 54, 56, 312; ICH E6). Applicable ICH guidelines on statistical methods and choice of control group were followed (ICH E9; ICH E10).

The pivotal study 499E01 sites were inspected by FDA with satisfactory outcome of the inspection.

II.4 Type of application and other comments on the submitted dossier

Legal basis
This application is submitted in accordance with an Article 8(3) from Directive 2001/83/EC (a new product/substance not yet authorised in the EU community).

Recothrom was approved in the USA by FDA on 17 Jan 2008 and was launched in the USA the same month.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

One major objection was identified by the CHMP concerning the specification of the potency assay of the drug product. The proposed broad potency specification was not supported by the batch data and it was requested that it should be tightened. The applicant, in their response, has confirmed that no more than a 10% loss of activity is observed over a 3 years storage period, as such they have proposed the shelf is extended to 3 years, which is supported by the stability data provided, and have defined a 10% overage in total activity at the time of filling as the lower limit for total clotting activity. The upper limit has been calculated based on manufacturing capabilities resulting in tighter overall potency limits which better reflect the potency of those batches used in clinical studies. This objection has been satisfactorily addressed, however the corresponding specification for specific activity has not been revised. This should be addressed because its calculation is determined based on the total activity and protein concentration of the final product, however this is not considered a major objection. In use stability of the product has only been assessed on product after 24 months storage. This study should be repeated using product stored for 36 months, however given the stability data provided thus far, the additional 12 months storage is not considered likely to impact significantly on the in-use stability, as such this data can be provided as a post approval commitment.

Following the assessment of the D120 responses there are still some outstanding issues relating to a few other concerns. However, overall the CHMP agreed that from a quality point of view the product could be approved provided satisfactory responses to the day 180 list of outstanding issues (LoOI) are given.

The overview below details the remaining issues to be addressed.

Drug Substance

Description of the drug substance
Recombinant human thrombin (rhThrombin), topical, is a coagulation factor produced via recombinant DNA technology from a modified Chinese hamster ovary (CHO) cell line. Recombinant thrombin is identical in amino acid sequence and structurally similar to naturally occurring human thrombin.

Recombinant Thrombin is generated from a recombinant fragment of prothrombin called recombinant human Prethrombin-1 (rPrethrombin-1). The coded sequence for the rPrethrombin-1 precursor is an N-terminally truncated variant of the naturally occurring prothrombin.

Manufacture

In accordance with ICH guideline Q5D, the applicant has established a two-tiered cell banking system consisting of a master cell bank MCB as a common starting source for production and a working cell bank (WCB). The applicant was asked to discuss further the comparability of assays used to determine copy number in the MCB and post production cell bank (PPCB), to give assurance that the copy number is not significantly falling during manufacture. This was not resolved in the responses.

rhThrombin manufacturing process for bulk drug substance (BDS) is broadly divided into 3 phases. In the first phase, recombinant human prethrombin-1 (rPrethrombin-1) is produced by a fed-batch cell culture process. In the second phase, the rPrethrombin-1 is recovered from the cell culture harvest and purified to generate the rPrethrombin intermediate. In the third phase, the rPrethrombin intermediate is converted to Thrombin alfa, which is then purified chromatographically and formulated to bulk drug substance (BDS).

The applicant has satisfactorily addressed most of the questions raised in relation to the manufacturing process and process validation, however there are still a few outstanding issues that should be discussed further.

Drug Product
The Thrombin alfa (rhThrombin) drug product 5000 IU or 20,000 IU is a sterile, lyophilised white to off-white solid or powder without preservatives. It is presented in 8 ml or 20 ml Ph. Eur. type I borosilicate glass containers closed with bromobutyl rubber stoppers and a flip-off overseal. The choice of excipients (all of Ph. Eur. quality) and their quantity is justified and acceptable.

rhThrombin DP 20,000 IU is identical in its presentation to the 5000 IU, except a larger vial and fill volume is used (20 ml).

Manufacture of the product
Bulk drug substance is shipped from the USA and drug product is manufactured in Europe in a validated, straight forward process which includes thawing and pooling of BDS bottles, the formulation (essentially a dilution in histidine buffer), sterile filtration, filling, freeze-drying and packaging process. The release of the drug product and final packaging and labelling is in the responsibility of Bayer Schering Pharma AG, Berlin.

The applicant has satisfactorily addressed the questions raised in relation to the manufacture of drug product and the product specifications.

Solvent
The solvent (0.9% Sodium Chloride) is a standard buffer, which is filled into polyethylene ampoules. The manufacturer, is well established, and GMP compliance has been demonstrated. Given the fact that product is filled in non-standard ampoules, and the limits this material has on moist heat sterilisation, re-validation of the sterilisation process has been undertaken. The validation data demonstrates sufficient

sterility assurance, however some results tables were missing from the report in the original submission and data relating to the validation of buffer preparation or the filling process was requested. This information has been provided in the responses and confirms the process of manufacture has been suitably validated.

TSE compliance

Compliance with Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMEA/410/01 rev 02) has been sufficiently demonstrated. The active drug substance of Recothrom is produced in serum-free culture medium. No material from human and animal species with TSE risk is added during the fermentation of Recothrom.

Virus safety

The fermentation process of the Recothrom is in a serum-free medium without use of human or animal derived components which minimises a possible contamination for adventitious viruses.

The cells used for production of Recothrom have been extensively screened for viruses. These tests failed to demonstrate the presence of any viral contaminant in the cells used for production of Recothrom with the exception of intracellular A-type and C-type retroviral particles. Such particles are well known to be present in hamster CHO cells. This is acceptable since there is excess capacity within the manufacturing process of Recothrom for reduction of this type of viral particles. Therefore, there are no concerns for the cell banks used in the production process of Recothrom.

An MVM test is routinely performed at the end of the fermentation runs and harvest material is screened for the presence of adventitious viruses using a panel of different cells lines and TEM analysis. The purification process of Recothrom includes several steps for inactivation/removal of viruses. The effectiveness of these steps has been demonstrated for a panel of enveloped viruses and small non-enveloped viruses.

In summary, virus safety has been sufficiently demonstrated.

GMP compliance

With the day 120 LoQ an inspection request was posed to confirm GMP compliance of all contract laboratories involved in manufacture and testing of active substance or drug product. GMP certification has been provided for the manufacturer of drug substance, as such GMP compliance can be assured. The EMEA has requested a routine re-inspection of this site also. Quality agreements between the manufacturer and subcontractors are expected to be reviewed during re-inspection.

Current GMP certification for the manufacturer of drug product has now been provided.

III.2 Non clinical aspects

The Applicant has conducted a programme of non-clinical studies for thrombin alfa (rhThrombin).

The nonclinical testing strategy for rhThrombin was based on:

- *In vitro* biochemical and coagulation investigations to demonstrate rhThrombin´s pharmacological efficacy in comparison to human plasma-derived thrombin including its interaction with thrombin inhibitors;
- *In vivo* haemostatic efficacy models conducted to characterise rhThrombin´s activity in reducing time to haemostasis in various surgical settings and to select an efficacious concentration for the clinical product;

- *In vivo* investigations into rhThrombin´s biodistribution, inhibitor-binding and clearance characteristics instead of conventional pharmacokinetic studies;
- Toxicological studies that included single-dose studies with topical administration in a wound-healing surgical model, repeated-dose toxicity studies, investigations into immunogenicity of the drug product, local tolerance studies and cytotoxicity studies;
- Investigation of the toxicity, including neurotoxicity, of prothrombin activator.

Pharmacology
The pharmacology of rhThrombin was characterised using investigations of *ex vivo* plasma clotting and *in vivo* haemostatic activity supporting an indication of an aid to haemostasis during surgery. No secondary pharmacodynamic or specific safety pharmacology studies were conducted.

rhThrombin was shown to induce clotting *ex vivo* in the plasma of rats, rabbits, cynomolgus monkeys and humans. Clotting times were 7.5 ± 0.1 seconds for rabbits, 9.3 ± 0.1 seconds for rats, 9.5 ± 0.1 seconds for humans and 13.8 ± 0.2 seconds for cynomolgus monkeys. Additional studies examining kinetic rate constants using peptide substrates demonstrated that rhThrombin achieved the same enzymatic kinetic rate as human plasma thrombin. In a hepatic bleeding injury model of diffuse bleeding in the rabbit, concentrations of 500 U/mL and above led to reduced time to haemostasis (TTH) when compared with saline. In a rat heminephrectomy model including arterial bleeding, TTH for thrombin alfa (at doses >1000 U/mL) was significantly different from that for saline ($p < 0.005$)). rhThrombin at concentrations higher than 100 U/mL was more effective at reducing blood loss than saline alone. The efficacy of thrombin alfa topically delivered via the proposed spray applicator in the absence of a passive haemostat was demonstrated in a porcine, partial-thickness, excisional skin wound model. rhThrombin resulted in a 25–57% reduction in TTH.

Pharmacological and pharmacodynamic comparability were shown between pilot-scale and commercial-process materials, including in studies of *in vitro* binding of rhThrombin from the pilot and commercial processes to purified thrombin inhibitors, anti-thrombin III (ATIII) and α-2-macroglobulin (α2M).

No adverse effects of rhThrombin were observed in a general behavioural screen following repeated dosing of cynomolgus monkeys via the subcutaneous route of administration at doses up to 346 U/kg.

In response to a clinical question, an additional non-clinical study using the rat heminephrectomy model was conducted to compare the performance of rhThrombin with that of Evithrom, (eTh; containing the same human plasma-derived thrombin as in Evicel) in combination with the Gelfoam (GF) absorbable gelatin sponge. Topical application of either type of thrombin + GF produced haemostasis more rapidly than saline + GF. A significant reduction ($p<0.0001$) in median TTH was observed in animals treated with eTh + GF (70 seconds) or rhThromnbin + GF (46 seconds), as compared with the saline control group (134 seconds). It was concluded that rhThrombin has the same efficacy as human plasma-derived thrombin in the rat heminephrectomy model. It is accepted that these data can be extrapolated to the clinical situation.

The model used was very similar to the type of bleeding that would occur in surgery in patients, and the product showed good activity. The fact that the product is based on the human protein, with an identical amino acid sequence, yet still worked in the rat model supports the view that the model is predictive of what may happen in clinical situation. This is further supported by the fact that the comparator, thrombin derived from human plasma, also showed activity.

Pharmacokinetics
Traditional absorption, distribution, metabolism and excretion (ADME) studies were not performed.

Endogenous thrombin is cleared by two separate pathways: 1. rapid formation of thrombin inhibitor complexes, which are recognised by hepatic receptors and degraded, and 2. direct binding to

thrombomodulin on the endothelium, followed by internalisation and degradation. Known thrombin inhibitors include ATIII, α2M and heparin cofactor II.

The pharmacokinetics of rhThrombin were investigated using ^{125}I-labelled rhThrombin. The fate of thrombin alfa regarding its rapid complexing with thrombin inhibitors in plasma and its degradation has been characterised in animal models using topical application in a wound model and after intravenous (IV) (3.5 U rhThrombin/kg) and subcutaneous (SC) (350 U rhThrombin/kg) administration. In the latter study, rhThrombin was rapidly complexed.

Based on noncompartmental analysis, rhThrombin-equivalents had similar pharmacokinetic indices following either IV or SC administration, and SC bioavailability of approximately 95%. Following IV administration, rhThrombin equivalents exhibited an initial half-life (t1/2, initial) of 0.17 h (10.2 min). Following either IV or SC administration, rhThrombin had a terminal half-life (t1/2, λz) of approximately 15 h, probably reflective of the elimination of formed inhibitor complexes and their degradation products. Size exclusion (SE)-HPLC analysis revealed that [^{125}I]-rhThrombin was rapidly complexed to ATIII and other inhibitors in the systemic circulation. The only measurable non-complexed [^{125}I]-rhThrombin was found at 5 minutes postdose following IV administration. At later time points, only [^{125}I]-rhThrombin complexes and free [^{125}I] were measurable. Based on trichloroacetic acid-precipitation data and the IV SE-HPLC results, it appears that following either IV or SC administration to male cynomolgus monkeys, rhThrombin binds to endogenous inhibitors and is then eliminated.

Following SC dosing in cynomolgus monkeys, radioactivity was primarily observed in the region of the SC dose site up to 6 hours post-dose. Test article-associated radioactivity was primarily observed in the region of the liver/spleen up to 24 h following IV dosing and after 6 h following SC dosing.

Following application of a ^{125}I-thrombin alfa-saturated Gelfoam sponge to a liver wound in rabbits, minimal radioactivity was detected in plasma samples collected from 5 minutes to 24 hours post-application and little radioactivity was found at a site distal (on a separate liver lobe) to the application site. Less than 0.37% of the total administered thrombin alfa dose was accounted for in the total plasma volume at any measured time point but it could not be established whether the ^{125}I-thrombin alfa was complexed or uncomplexed.

Anti-thrombin alfa antibodies were not detected in either a single-dose wound-healing study in cynomolgus monkeys or in a multiple-dose safety study by the SC route.

Toxicology

The safety studies with rhThrombin include single-dose toxicity in rabbits and single- and repeated-dose toxicity in cynomolgus monkeys. The choice of these species was justified on the basis of the *ex vivo* plasma clotting studies. Local tolerance has been assessed in two studies and an *in vitro* cytotoxicity study has also been conducted. Prothrombin activator (PTA) is used to convert rhPrethrombin-1 to active thrombin alfa enzymatically. The potential for toxicity resulting from the residual PTA in rhThrombin has been studied in mice, and a risk assessment of potential neurotoxic PTA impurities has been provided.

No studies have been conducted on genotoxicity, carcinogenicity, reproductive and developmental toxicity or juvenile toxicity. This is acceptable for a product of this type.

rhThrombin was shown to be safe and well tolerated in systemic toxicity studies in the rabbit and cynomolgus monkey. The pivotal studies conducted in cynomolgus monkeys demonstrated no evidence of toxicity or altered wound healing when thrombin alfa was applied with an absorbable gelatine sponge to a surgical liver wound. In addition, thrombin alfa was well tolerated in cynomolgus monkeys that received weekly SC injections over 4 weeks, with no signs of local or systemic toxicity. In both studies, evaluation of plasma coagulation indices, haematology, serum chemistry and gross and microscopic pathology revealed neither evidence of local or systemic activation of the coagulation cascade nor secondary signs of

activation of the coagulation system such as ischemia, thrombosis, fibrin deposition or thrombus formation. Using a nominal no observed adverse effect level (NOAEL) of 1500U, low but acceptable safety margins of between 0.875 and 3.5 depending on the clinical dose were demonstrated.

Studies prescribed under the ISO Guideline for Medical Devices showed that rhThrombin was non-irritating when applied topically to normal or abraded skin (100 – 2000 U/mL), or when instilled into the eyes of rabbits (100 – 2000 U/mL). In addition, results from an *in vitro* cytotoxicity assay using mouse L929 cells demonstrated no primary cytotoxic effects.

Cynomolgus monkeys treated with rhThrombin demonstrated no significant or sustained antibody formation to rhThrombin, and a low incidence of low-titre antibody formation against PTA or impurities from the Chinese Hamster Ovary cells used in the production process.

In mice, PTA dosed intravenously produced no test article-related effects at 0.0005 mg/kg, transient and acute adverse behavioural and physical observations at doses of 0.0025 mg/kg, and overt toxicity at ≥0.0075 mg/kg consistent with the known procoagulant activity of PTA. No test article-related toxicity was present after single or repeated SC doses of 1.0 mg/kg PTA. However, repeated SC injection of PTA resulted in anti-PTA antibody formation in BALB/C mice. Based on the single-dose IV toxicity study, there is a safety margin of greater than 100 compared with the estimated human exposure at a high clinical dose.

A risk assessment for potential neurotoxic impurities derived from the purified PTA was conducted and it was concluded that if the most neurotoxic constituent were contaminating thrombin alfa drug product at the upper release specification limit of 20 ng/mg rhThrombin, contributing to 100% of all impurities and assuming a very high thrombin alfa clinical dose (i.e. 40,000 IU, based on clinical experience gathered so far), the maximum hypothetical level of neurotoxin is 547-fold below the estimated human LD_{50}. Based on the currently determined levels of the PTA impurities in thrombin alfa bulk drug substance (<1 ng/mg) and assuming that 100% of the PTA relates to the toxin, the level is 10,938-fold below the estimated human LD_{50}.

A risk assessment for potential thrombogenicity was conducted and it was concluded that it has been shown that rhThrombin acts locally, does not enter the blood stream to any great extent and is inactivated by the thrombin inhibitors in the blood stream. There was no evidence in the toxicity studies of activation of the coagulation system.

Use of rhThrombin is not expected to pose a risk to the environment.

Rapporteurs consider that the applicant has conducted an acceptable programme of toxicity studies on the active substance and potential contaminant PTA. The duration of the repeat-dose studies is adequate to support a marketing authorisation and there is no need for any more studies of any type to be conducted.

rhThrombin was generally well tolerated under a regimen of weekly subcutaneous dosing at 346 U/kg for 4 weeks in cynomolgus monkeys. Adequate margins of exposure over the human clinical exposure have been demonstrated. No target organs were identified and there was no delayed toxicity after dosing had stopped. Adequate safety margins for the potential contaminant PTA have been shown and a risk assessment for neurotoxicity also revealed an acceptable estimated safety margin.

Non-clinical evidence for comparison against the placebo

New non-clinical study was conducted and confirmed that Recothrom had a similar effect to that of human plasma derived thrombin. The study description was clear and it appears to have been conducted to a satisfactory standard. The potential for confounding of the results by variables such as body weight and mean arterial pressure was adequately controlled. Both products had statistically significantly shorter

times to haemostasis than the control treatment (saline). In this respect, they can be judged to have behaved similarly.

From a non-clinical perspective, the Applicant's view is supported that the study has demonstrated the therapeutic usefulness of the Recothrom in that its performance was similar to that of human plasma-derived thrombin against placebo. It is accepted that these data can be extrapolated to the clinical situation.

III.3 Clinical aspects

Pharmacokinetics & Pharmacodynamics
There were no formal PK/PD studies conducted by the applicant. This is appropriate for this type of product. Thrombin is well characterised substance, which is rapidly neutralized by naturally circulating plasma inhibitors limiting its duration of action and preventing the active form from diffusing into the general circulation.

Clinical efficacy
Dose finding studies dose rationale
An initial phase I study (499C05 Part I) in spinal surgery examined 3 concentration levels of thrombin alfa (250, 500, and 1000 IU/mL). There was no dose-limiting safety observations at any of the concentrations studied. At the same time, the dose dependent plateau was observed with no further improvement of haemostasis with concentration levels > 1000 IU/mL. In addition, the applicant referred to non-clinical and toxicology studies to support the tolerability of the dose 1000 IU/ml. The latter dose was taken into phase II-III development. However the dose-finding strategy was not sufficiently justified since only marginal differences were seen between placebo and Recothrom in terms of attainment of TTH. Individual doses between 1 mL and 48 mL have been used in the clinical trials. The upper volume limit should be clearly defined for each different type of surgery. The dose variability identified in different surgical settings correlated with size of the surgical intervention and bleeding rate. In addition, slightly higher quantities utilised in burn surgery were related to use of spray applicator as the size of burn wound required larger volumes of reconstituted product to achieve the haemostasis.

Main clinical studies
Pivotal 499E01 study
Method and conduct
The phase III, randomized, double-blind, controlled, comparative efficacy and safety study of topical recombinant human thrombin (rhThrombin) and Thrombin-JMI (Bovine Thrombin) in surgical haemostasis was conducted at 34 sites in the United States. The study included 4 surgical settings: spinal, hepatic, PAB (peripheral artery bypass) surgery patients and patients undergoing AV graft formation for haemodialysis.

The study was planned as non-inferiority comparative trial with 15% non-inferiority margin for the difference in the incidence of haemostasis within 10 minutes between bovine thrombin and thrombin alfa chosen based on a recommendation from the FDA during the conduct of the study.

Endpoints
The primary endpoint was TTH, summarized as the incidence of haemostasis within 10 minutes.

Secondary endpoints included health outcomes: duration of the surgical procedure from incision to closure; total length of hospital stay; use of alternative topical haemostatic agents at the TTH evaluation sites; use of blood products, including recombinant human clotting factors (e.g., packed red blood cells, Factor VIII, or platelets); need for re-operation for bleeding or thrombotic complications; immunogenicity and safety measurables.

Comparator:
Thrombin alfa was compared to an active comparator, bovine Thrombin (Thrombin-JMI).
The Applicant argued, that from an ethical point of view the surgeon investigators considered it was not acceptable to perform a large placebo-controlled trial in phase III without allowing the provision of an active rescue therapy. The administration of active rescue therapy would have confounded the study results, especially for the placebo-treated subjects switching to active medication and care had to be taken that subjects treated with thrombin alfa would not receive bThrombin. The double-blinded design did not allow using other comparators, e.g. argon beam, fibrin glue etc. The Applicant is of the opinion, that Thrombin-JMI as a comparator can be justified on the basis of other fibrin sealant products available in the EU.

The single pivotal study does not fulfil the EU requirements according to the 'Guideline on the clinical investigation of plasma derived fibrin sealant/haemostatic products (CPMP/BPWG/1089/00)' and the 'Core SPC for Plasma derived Fibrin Sealant/Haemostatic Products (CPMP/BPWG/153/00)': In analogy to fibrin sealants which should be compared to standard treatment without fibrin sealant, a thrombin product should be compared to standard treatment without haemostatic component. The demonstration of non-inferiority to bovine thrombin does not fulfil this requirement. A comparison to gelatine sponge plus saline (placebo), as done in the Phase II trials with Recothrom, is reasonable, feasible, and necessary to provide sound data for clinical efficacy. It is also considered ethical since the sponge itself provides evidence for haemostatic efficacy. Rescue treatment should in any case be offered, but should be chosen without thrombin.

By investigating a wide range of surgeries (spinal surgery, hepatic resection, PAB, and AV graft formation for hemodialysis access), the Applicant sought to demonstrate clinical efficacy of thrombin alfa in general surgery in order to apply for the general hemostasis labelling claim "for supportive treatment in surgery for improvement of haemostasis".

However, according to the 'Core SPC for plasma derived fibrin sealant/haemostatic products (CPMP/BPWG/153/00)' approval for 'general hemostasis' does not allow to use Recothrom in vascular surgery or in neurosurgery. These are separate, special indications called "suture support in vascular surgery" and "for tissue adhesion /sealing and suture support in neurosurgery and surgical procedures where contact with cerebro-spinal fluid or dura mater can occur"; for which separate adequately powered clinical trials are required.

Most of the surgical settings investigated in the pivotal study, namely peripheral arterial bypass surgery, arteriovenous graft formation and spinal surgery, are therefore not representative to support the claimed indication 'general hemostasis'.

Results
463 subjects were randomly assigned to treatment (rhThrombin, n=231; bThrombin, n=232). Of enrolled subjects, 411 received study treatment (rhThrombin, n=205; bThrombin, n=206). Most of the subjects who received study treatment completed the protocol (overall n=401, 98%; rhThrombin, n=201, 98%; bThrombin, n=200, 97%). Reasons for not completing the protocol were generally balanced between overall treatment groups. The primary efficacy analysis was conducted in ITT, per protocol (PP) and exploratory populations. Sensitivity analysis with conservative treatment of missing values was provided as well.

Demographic characteristics in phase III by surgery type are summarised below:

Parameter	Category/Statistic	Spine (N=122)	Hepatic (N=125)	PAB (N=88)	AV Graft (N=76)
Age (year)	Mean (SD)	56.0 (13.4)	55.6 (15.8)	65.0 (9.8)	62.1 (13.2)
	Median	54.5	57.0	65.0	60.5
	Min, Max	24, 86	21, 89	43, 88	28, 86
	≥65 years, n (%)	35 (29)	39 (31)	48 (55)	31 (41)
	≥75 years, n (%)	14 (11)	18 (14)	15 (17)	14 (18)
Gender, n (%)	Male	54 (44)	67 (54)	57 (65)	38 (50)
	Female	68 (56)	58 (46)	31 (35)	38 (50)
Race, n (%)	Asian	3 (2)	12 (10)	0	1 (1)
	Black or African American	5 (4)	8 (6)	20 (23)	43 (57)
	Hispanic	4 (3)	12 (10)	1 (1)	16 (21)
	Native Hawaiian/Pacific Islander	0	2 (2)	0	0
	White	110 (90)	87 (70)	67 (76)	16 (21)
	Other	0	4 (3)	0	0

Abbreviations: AV = arteriovenous; PAB = peripheral arterial bypass; SD = standard deviation

Results of primary efficacy analysis from 499E01 study are summarised in the table below (ITT population):

Bleeding Site Type	Observed bThrombin n/N (%)	Observed rhThrombin n/N (%)	Observed Treatment Effect[1] % (95% CI)	Modeled bThrombin %	Modeled rhThrombin %	Modeled Treatment Effect[2] % (95% CI)	Adjusted Treatment Effect[3] % (95% CI)
Overall	193/203 (95.07)	189/198 (95.45)	0.38 (–3.78, 4.54)	95.11	95.42	0.31 (–3.73, 4.35)	0.32 (–3.73, 4.35)
Epidural	60/61 (98.36)	60/61 (98.36)	0.00 (–4.51, 4.51)	98.4	98.4	0.00 (–4.51, 4.51)	
Hepatic	61/63 (96.83)	61/62 (98.39)	1.56 (–3.78, 6.91)	96.8	98.4	1.56 (–3.78, 6.91)	
PAB Proximal	36/42 (85.71)	34/40 (85.00)	–0.71 (–16.03, 14.60)	85.7	85.0	–0.71 (–16.03, 14.60)	
AV Graft Arterial	36/37 (97.30)	34/35 (97.14)	–0.15 (–7.75, 7.45)	97.3	97.1	–0.15 (–7.75, 7.45)	

1 Treatment effect = (rhThrombin) – (bThrombin). 95% CI is Wald interval for difference in proportions

2 Treatment effect = (rhThrombin) – (bThrombin). A linear model with treatment group, four primary bleeding site types, and the interaction between treatment group and bleeding site type as covariates was used to compare rhThrombin to bovine thrombin. 95% CI is Wald interval. Each of the four bleeding site types is weighted by subject enrollment in the primary efficacy analysis population

3 Bias-adjusted mean estimator of modeled treatment effect and 95% CI adjusted by sample mean ordering method are provided

Denominators are the number of randomized subjects who received blinded study drug at one of four primary bleeding sites

Both treatments achieved a high incidence of haemostasis within 10 minutes (rhThrombin n=189/198, 95.4%; bThrombin n=193/203, 95.1%). The incidence was 0.3% greater for rhThrombin than for bovine thrombin (95% CI –3.7 to 4.4). The lower bound of the 95% confidence interval of the difference (rhThrombin-bThrombin) was –3.7%, which excluded the value of –15%. Thus, the treatments have comparable efficacy. Overall 95%CI were within 10% and 5% non-inferiority boundaries. However, the efficacy in PAB proximal surgery appeared to be inferior with lower bound margin exceeding -15%. Similar results were seen with PP and exploratory dataset analyses. The lower bound margin for 95%CI in PAB was below the margin of 15% and extended further low from ITT to PP and exploratory set analyses. The lower margin extended below 19% in the sensitivity analysis of PAB surgery results using a conservative interpretation of missing values. The applicant explains this with a high variability due to small sample size in PAB surgery, high use of anticoagulant/anti-platelet medicines and especially challenging haemodynamic settings (high pressure flow at anastomotic sites). The sensitivity analysis using a conservative interpretation of missing and censored TTH values confirmed the robustness of the primary efficacy analysis results in terms the overall 95%CI (all surgical types).

Considering all 4 surgery types in the pivotal 499E01 trial, the non-inferiority of rhThrombin to bovine thrombin was demonstrated.

The applicant conducted additional sensitivity analyses of the primary endpoint in relation to placebo with a statistically significant difference overall across all types of surgeries: 13.2% (95% confidence interval:

3.4% - 23.0% *P*=0.0081). The superiority could not be demonstrated in individual surgeries as confidence intervals crossed a zero in all cases However, the results are more pronounced in AV surgery (only -0.7% as lower bound CI), but did not reach statistical significance for other surgeries. It is noted that the non-inferiority against bovine thrombin was not met in PAB surgery. The product should not be used in specialised surgeries and in fact since the non-inferiority has not been demonstrated in PAB surgery, an appropriate wording is proposed in section 4.1 of the SmPC.

The applicant conducted the meta-analysis from 3 pivotal studies used in support of licensing applications of EU approved fibrin sealants. Findings from meta-analysis are considered to be supportive. The results indicate that the overall magnitude of efficacy with Recothrom found in non-inferiority settings is comparable to the efficacy established against placebo with other licensed in EU fibrin sealant products (with up to 85-95% of the haemostasis incidence at 10 min at the primary site). Therefore results from 499E01 study are in line with haemostatic efficacy of other licensed fibrin sealants.

The following are aspects of ***conservatism*** in the Recothrom clinical program:

- Surgical settings such as AV graft, spinal, PAB surgery and hepatic surgery are characterised with severe intra-operative bleedings which are difficult to control due to limited access (spinal surgery) or due to diffuse and friable nature of the organ (liver). Placement of suture or ligature is non-practical in these situations due to the adjacency of critical structures (bile ducts, spinal arteries, hepatic arties and portal vein) and due to friable and delicate structure of organs involved (spinal surgery, vascular surgery and liver);

- Severe and diffuse bleeding from broad surface areas during and immediately following liver surgery (particularly in cirrhotic patients or patients with liver metastases) and patients who were coagulopathic – the latter cohort of patients was included in 499E01 study.

In response to a Major Objection on lack of comparison to the placebo, an additional non-clinical study was carried out with a significant reduction ($p<0.0001$) in median TTH observed in animals treated with human plasma derived thrombin+ Gelfoam (70 seconds) or rhThrombin + Gelfoam (46 seconds), as compared with the saline control group (134 seconds). It is accepted that these data can be extrapolated to the clinical situation and considered supportive.

Clinical studies in special populations

No studies were performed. In the phase III clinical study, 37% of subjects were ≥65 years, and 15% were ≥75 years. There was a slightly lower incidence of haemostasis within 10 minutes in elderly subjects compared to younger subjects (especially in proximal PAB surgery).

Supportive studies

Phase I-II studies

Phase	Study No	Subject Population	Primary Objective	Treatments Studied [Application mode]	Thrombin alfa N[a] /n[b] (n[c])	Total N[d]
I	499C05 Part I	Spinal surgery	Evaluate the safety of thrombin alfa	thrombin alfa (3 concentrations) [gelatin sponge]	9 / N/A(N/A)	9
II	499C05 Part II	Spinal surgery	Evaluate the safety of thrombin alfa	thrombin alfa; placebo [gelatin sponge]	33 / 21 (12)	42
	499C06	Hepatic resection	Evaluate the safety of thrombin alfa	thrombin alfa; placebo [gelatin sponge]	17 / 14 (3)	28
	499C07	PAB surgery	Evaluate the safety of thrombin alfa	thrombin alfa; placebo [gelatin sponge]	17 / 12 (5)	27
	499C08	AV graft formation for hemodialysis access	Evaluate the safety of thrombin alfa	thrombin alfa; placebo [gelatin sponge]	21 / 17 (4)	33
	499E02	Autologous skin grafting following burn injury	Evaluate the safety of thrombin alfa	thrombin alfa [Spray applicator]	72 / N/A(N/A)	72
				Phase I/II total:	169	211

The supportive controlled phase II studies had similar to phase III trial inclusion/exclusion criteria and evaluated the same parameter (TTH) as a secondary objective. Demographic and other baseline characteristics in the phase II studies were similar to those in phase III trial. However, the main objective of the controlled phase II studies was the evaluation of the safety and immunogenicity of thrombin alfa. The difference between pivotal phase III and phase II studies was the comparator: thrombin alfa versus placebo in combination with gelatine sponge; and studies were small and not powered to demonstrate the efficacy. However, results were supportive, with a numerically greater incidence of haemostasis within 10 minutes in the thrombin alfa group.

Consistent with the phase III estimates, the incidence of haemostasis in subjects undergoing PAB in phase II 499E07 study was lower than in the other 3 types of surgery. This was explained by the applicant to be a consequence of the high percentage of anticoagulant or anti-platelet medication usage in this group relative to subjects undergoing other types of surgery, and the high-pressure blood flow at the PAB anastomotic sites.

Incidence of haemostasis ≤10 minutes in rhThrombin-treated subjects by surgery (Phase II-III)

	Phase III		Phase II	
	n/N	% (95% CI)	n/N	% (95% CI)
Spinal surgery	60/61	98 (91, 100)	18/21	86 (64, 97)
Hepatic surgery	61/62	98 (91, 100)	14/14	100 (77, 100)
PAB surgery[a]	34/40	85 (70, 94)	10/12	83 (52, 98)
AV graft[b]	34/35	97 (85, 100)	16/17	94 (71, 100)

a Proximal anastomosis only
b Arterial anastomosis only
Abbreviations: AV = arteriovenous; CI = confidence interval; PAB = peripheral arterial bypass

The phase II studies compared safety and efficacy of Thrombin alfa with placebo, but they were not powered to demonstrate efficacy, which was only a secondary endpoint. Of note, in the phase II studies, the difference between placebo and Thrombin alfa with regard to haemostasis ≤10 minutes is not very striking: 80.4 % (53 of 66) of subjects treated with gelatine sponge + placebo reached haemostasis ≤10 min compared with 90.4 % (58 of 64) of subjects treated with gelatine sponge + Thrombin alfa; difference 10.5%, 95%-CI: -2.1% - 22.5%.

Most gelatine sponges were removed in the phase III study after reach of haemostasis.

Proof of efficacy on grounds of sound clinical data is missing. The placebo-controlled Phase II studies were not powered to evaluate efficacy differences between placebo and thrombin alfa. It is, however, of note, that especially in liver surgeries, the main field of the intended indication, only two treatment failures had been reported for (sponge plus) placebo treatment. Sponge plus thrombin alfa and sponge plus saline showed quite similar efficacy results in the small Phase II trial. Additionally, the reported differences in mean TTH between placebo and thrombin alfa are small: e.g. 12 seconds in epidural venous plexus (spinal) surgery and 30 seconds in hepatic resection surgery. These small differences in TTH do not considerably support the assumption that the use of thrombin alfa might lead to a true clinical benefit in the sense of shorter time in the operating room, better overall state after surgery, less need for blood transfusions, or faster recovery.
Further, in order to apply for spray administration, a clinical trial comparing sprayed thrombin alfa with sprayed placebo (saline) could have been feasible and relevant. The preclinical trial in the porcine excisional wound model can only be regarded as supportive, but is no alternate for an efficacy and safety study in human. Spray application is not sufficiently investigated by the uncontrolled Phase II study and is therefore not regarded approvable due to lack of proof of efficacy and safety in human.
Finally, the company initiated an additional study 499H04 (open, single-arm) study in children with burns. Therefore further clinical data on use of Recothrom in burn surgery will be available. There is a medical need for fibrin sealant products in burn surgery and especially in children with burns.

Clinical safety

Patient exposure

Phase	Study No	Number of subjects exposed to thrombin alfa (including subjects from phase II who switched from placebo to thrombin alfa due to rescue treatment)
I	499C05 (Part 1 = Phase I)	9[b]
II	499C05 (Part 2 = Phase II)	33[a]
	499C06	17[a]
	499C07	17[a]
	499C08	21[a]
	499E02	72[c]
III	499E01	205[a]
IIIb	499F04	209[a]
	Total	583

a 1000 IU/mL thrombin alfa to be administered in combination with absorbable gelatin sponge
b 3 subjects each exposed to 250, 500, or 1000 IU/mL open-label thrombin alfa + gelatin sponge
c In Study 499E02 a spray applicator was used

Each subject received thrombin alfa during one surgical procedure, although multiple sites of bleeding could be treated. All exposures occurred within a 1-day period.

In accordance with the size of surgical intervention and requirement for haemostasis, a wide range of doses between 1 and 48 mL of the reconstituted solution equivalent to 1,000 to 48,000 IU of thrombin has been used in the pivotal phase III study.

In the majority of subjects in the phase III study the absorbable sponge was removed from the bleeding site after reach of haemostasis. The follow-up of Thrombin alfa is therefore mainly reported for the situation without remaining gelatine sponge.

Adverse events, serious adverse events and deaths

Parameter	Phase III		Phase II controlled clinical studies		Phase II Study 499E02
	bThrombin (N=206)	Thrombin alfa (N=205)	Placebo (N=42)	Thrombin alfa (N=88)	Thrombin alfa (N=72)
Overall AE incidence, n (%)	205 (100)	204 (100)	42 (100)	88 (100)	63 (88)
Maximum severity of AEs[a], n (%)					
Mild	18 (9)	14 (7)	8 (19)	14 (16)	27 (38)
Moderate	116 (56)	106 (52)	28 (67)	57 (65)	24 (33)
Severe	65 (32)	73 (36)	5 (12)	15 (17)	11 (15)
Life threatening	4 (2)	10 (5)	0 (0)	1 (1)	1 (1)
Death	2 (1)	1 (<1)	1 (2)	1 (1)	0
Incidence of SAEs, n (%)	46 (22)	36 (18)	8 (19)	21 (24)	6 (8)
Deaths, n (%)	2 (1)	1 (<1)	1 (2)	1 (1)	0
Discontinuations due to AE, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0
Incidence of treatment-related AEs[b], n (%)	2 (1)	7 (3)	2 (5)	4 (5)	4 (6)
Total number of AEs	1295	1344	217	522	222
Mean number AEs per subject	6.3	6.6	5.2	5.9	3.5
Total number of SAEs	71	63	10	31	9
Mean number of SAEs per subject	0.3	0.3	0.2	0.4	1.7

a Maximum severity of AEs is summarized by subject.
b Possibly, probably, or definitely related to study drug as determined by the investigator.
Note: all events presented are treatment-emergent
Abbreviations: AE = adverse event: SAE = serious adverse event

The size of overall safety database is considered to be acceptable. Overall, the safety profile of Recothrom appears to be acceptable. There was no obvious imbalance in terms of the incidence in adverse events compared to bovine thrombin in the pivotal phase III study. Some procedural reactions (pain) and pruritis were reported. The incidence of hypersensitivity reactions in the pivotal phase III study was similar to the one observed with bovine thrombin.

The analysis of thrombotic or bleeding events incidence and the risk of infection did not show any obvious imbalance between rhThrombin and bovine thrombin.

4 cases of myocardial infarctions were reported in 499E01 study in patients treated with Recothrom: with 1 case in PAB surgery, 2 in spinal surgery and 1 in hepatic surgery. All 4 cases were reported on Day 2-3 following surgery and were reported in patients with multiple previous risk factors including arteriovascular disease, previous MI, peripheral artery disease etc. There were no cases of myocardial infarctions in bovine thrombin treated groups in all four surgeries. An additional open uncontrolled study 499F04 (conducted as a part of commitment to FDA) contained 3 additionally reported cases of MI. Amongst these 3 new cases only one case occurred on Day 3 following surgery. 2 other cases occurred more than 1 week after surgery in distant post-operative period. Again all three cases occurred in patients with multiple risk factors and baseline preponderance to myocardial ischemia. Overall, the incidence of all cardiac and thrombotic events between groups across all studies was similar. Therefore the incidence of myocardial infarctions is considered as a chance finding. An intensive PSUR surveillance and other risk minimisation steps were proposed to address the risk and enable to collect further data in the post-marketing period. In addition, a warning on use of the product in patients with baseline risks of stroke and myocardial infarction was implemented in section 4.4 of SmPC.

There were 5 death reports across all submitted studies. 2 cases of death were reported specifically with use of rhThrombin. All these deaths occurred with interval of time from the day of surgery itself and considered to be unrelated to use of thrombin. 2 additional deaths unrelated to Recothrom and remote to days immediate to the surgery were reported in anti-thrombin-seronegative patients in 499F04 study (phase IIIb).

Laboratory findings
In general, laboratory results (haematology, coagulation parameters, and blood chemistry) were as expected for a surgical population and were comparable between bovine thrombin and rhThrombin treatment groups in each type of surgery.

Immunological events
In phase III trial, hypersensitivity reactions were similar between treatment groups (rhThrombin, n=30, 15%; bThrombin, n=37, 18%). Overall, the incidence of antibody reactions following treatment of thrombin alfa was low both in phase III (1.5%) and in phase II controlled studies (1.2%), and was comparable to the rate observed with placebo in phase II (2.4%). None of the subjects developing antibodies to thrombin alfa had associated abnormal coagulation laboratory parameters (PT, INR, or aPTT) or clinically relevant sequelae. There was no obvious difference in antibody development between phase II and phase III studies despite some manufacturing changes that were implemented throughout the clinical development program resulting in consequential changes in post-translational characteristics of the rhThrombin. The detection of anti-Thrombin alfa antibodies at baseline (controlled phase II studies: 7/130, 5.4%; non-controlled phase II: 1/70, 1.4%; phase III: 3/198, 1.5%) was not accompanied with further increase of antibody titre and did not result in any clinically relevant adverse events. The company is undertaking a further study in re-exposure to Recothrom to explore the immunogenicity of the product.

Summary of anti-bThrombin and anti-thrombin alfa antibody status in the phase III study

	bThrombin (N=206)	thrombin alfa (N=205)	*P*-value
Evaluable subjects, n	200	198	
Detectable at baseline, n (%)	10 (5)	3 (1.5)	
Antibody development, n (%)[a]	43 (22)	3 (1.5)	<0.0001
95% CI	(16, 28)	(0, 4)	

a Defined as seroconversion or ≥1.0 titer unit (≥10-fold) increase in antibody level postbaseline

New phase IIIb data enhancing the immunogenicity database

With the responses to Day 120 LoQ, the company reported results of an additional phase IIIb open-label, single-group, multi-site study 499F04 study designed to evaluate the immunogenicity and safety of Thrombin alfa among subjects at increased risk for having anti-bovine thrombin product antibodies as a result of prior surgery with a high likelihood of bovine thrombin exposure. Topical Thrombin alfa (1000 IU/ml) was applied during a single spinal or vascular surgical procedure. Immunogenicity was evaluated by enzyme-linked immunosorbent assay at baseline and Day 29; safety measures were evaluated through Day 29. Subjects were eligible for participation if they had definite or highly likely prior exposure to bovine thrombin within the previous 3 years.

209 subjects (30-89 years, mean age 61 years) received topical treatment with Thrombin alfa. Subjects had undergone a mean of 6.2 prior surgeries, and previous exposure to bovine thrombin during the last 3 years was considered definite for 94 subjects (45%), highly likely for 114 subjects (55%), and was not known for 1 subject. The study included 89 subjects (43%) undergoing spinal surgery, 75 subjects (36%) undergoing arterial reconstruction or PAB, and 45 subjects (22%) undergoing an AV access procedure.

Anti-bovine thrombin product antibody status was assessed at baseline for 205 of the 209 subjects. Of the 205 subjects, 32 (15.6%) were seropositive and 173 (84.4%) were seronegative for baseline anti-bovine thrombin product antibodies. Seropositive subjects were, on average, older than seronegative subjects (mean age 65.8 years vs. 60.6 years) and had undergone more prior surgical procedures (mean number of prior surgical procedures = 7.9 vs. 5.9, seropositive vs. seronegative). A larger proportion of seropositive subjects underwent arterial reconstruction or PAB study surgeries (47% vs. 34%, seropositive vs. seronegative) and a smaller proportion underwent AV vascular access procedures (13% vs. 23%).

The immunogenicity analysis set included the 200 subjects who were treated with Thrombin alfa and had results from both baseline and post-baseline antibody assessments. In summary, no subject (n=0/200, 0%) became positive for anti-Thrombin alfa product antibodies during this study. The immunogenicity of Thrombin alfa was not affected by the presence of anti-bovine thrombin product antibodies.

This study demonstrates that a single dose of Thrombin alfa is minimally immunogenic, is well tolerated, and can be safely applied as an aid to haemostasis in patients with or without pre-existing antibodies to bovine thrombin product.

Ongoing re-exposure study

Another clinical trial addressing re-exposure of Thrombin alfa is currently being performed. The study will assess the safety and immunogenicity of a second treatment with Thrombin alfa in patients who have previously been treated in one of the clinical trials. It is expected that the study report will be available by March 2011.

Safety related to drug-drug interactions and other interactions

No differences were observed in the overall safety profile of subjects who did or did not receive anti-platelet, anti-coagulation, or thrombolytic medications during or before surgery, or between thrombin alfa and bovine thrombin treatment groups. As expected, there was an increased incidence of bleeding events in subjects receiving concomitant medications affecting coagulation, which was balanced between treatment groups, and therefore not specific to thrombin alfa.

Discontinuation due to AES

None

Post-marketing safety

Per the US periodic Report (interval ending 16 April 2009), a data aggregation inclusive of both post-marketing and clinical experience, there has been no emergent or potential safety signal identified for Recothrom to date since US product approval. There were no adverse event reports from spontaneous, regulatory or published literature sources.

The total exposure through 16 April 2009 included at least 166,834 based on the product utilization assumed to equal one unit per patient.

Pharmacovigilance system

The CHMP consider that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

Additional Pharmacovigilance
Studies to investigate paediatric population, thromboembolic risks and re-exposure are planned / ongoing.

There are outstanding issues with the Risk Management Plan, in relation to the proposed re-exposure study, educational materials and the proposed study to investigate thromboembolic events.

IV. ORPHAN MEDICINAL PRODUCTS

N/A

V. BENEFIT RISK ASSESSMENT

V.1 Benefits

Surgeons aim at achieving effective haemostasis during surgical procedures. For that reason surgeons use topical haemostatic agents as an adjunct to improve the surgical outcome. The applicant has evaluated the efficacy and the safety of Recothrom in four challenging and representative surgical settings representative major general surgeries and characterised by profuse bleeding and coverage of really high risk group of patients with serious co-morbidities (cardiovascular, chronic renal failure, immobility due to spinal problems etc.).

Spinal Surgery
Bleeding from the epidural space is frequently a significant clinical problem in subjects undergoing primary spinal surgery, including discectomy, laminectomy, and posterior or transforaminal lumbar interbody fusion (PLIF/TLIF). The epidural plexus of veins lies on the dura adjacent to the spinal cord and nerve roots, and the plexus is often disrupted during disc removal. Complete haemostasis must be obtained to avoid the possibility of hematoma adjacent to the spinal cord or nerve roots, which could lead to significant clinical sequelae. In order to avoid damage to the nerves from electrocautery or pressure, the use of fibrin sealants is considered as useful to control excessive bleeding.

Hepatic Resection
Uncontrolled bleeding from the cut surface of the liver following major hepatic resection can be a significant clinical problem. The relatively large surface area of the well-vascularized resection bed can result in significant intra-abdominal haemorrhage if adequate haemostasis is not achieved, especially as the hepatic sinusoids have no intrinsic smooth muscle to mediate vasoconstriction.

Peripheral Arterial Bypass Surgery
Systemic anticoagulation is required during peripheral bypass surgery, substantially altering the ability of a patient to form a clot. Suture line bleeding from an arterial anastomosis, especially when using a synthetic graft, provides an opportunity to evaluate diffuse bleeding that is currently managed by wrapping the anastomosis with an absorbable fibrin sealant products However the non-inferiority of Recothrom against the bovine thrombin *has not been demonstrated* and therefore the product should not be used in this type of surgery.

Arteriovenous Graft Formation for Haemodialysis Access
Construction of an arteriovenous graft for dialysis access often results in bleeding through the suture line in the synthetic graft at the site of the anastomosis. Electrocautery is not a viable alternative to prevent suture line bleeding, and additional sutures may narrow the anastomosis, which increases the incidence of failure of the graft/conduit. This clinical setting is complicated by uremic coagulopathy and by the use of

regional or systemic heparin. The suture line, except when there is a frank hole due to improper tension on the suture or poor stitch placement, results in diffuse bleeding that is often controlled by wrapping the anastomosis with absorbable fibrin sealants.

Recothrom (thrombin alfa) represents a first recombinant thrombin which can obviate the need for plasma derived products (both human plasma, bovine or porcine sources) associated with TSE and viral transmission risks and dependent on the plasma source availability. In addition, Recothrom does not contain aprotinin, which was linked previously with an increased cardiovascular mortality. As a consequence the availability of the fibrin sealant product without aprotinin, such as Recothrom is viewed as a benefit.

The clinical development program of topically applied thrombin alfa provides evidence that thrombin alfa as a recombinant product has an overall non-inferior efficacy to the bovine plasma derived product bThrombin. In addition, thrombin alfa offers the benefit of significantly lower rates of post-exposure immune response.

Thrombin alfa was tested in controlled clinical studies in surgical settings (spinal surgery, hepatic segment resection, peripheral artery surgery and arteriovenous graft formation) where profuse and diffuse bleeding often requires the use of adjunctive haemostatic treatment despite adequate surgical techniques. Thus, the settings studied as well as the study populations are typical and allow the extrapolation to other conditions, in which such therapy is needed.

In the phase III study thrombin alfa as well as the comparator bThrombin achieved haemostasis within 10 minutes in 95% of the subjects studied. These results were supported by 4 controlled phase II studies in the same surgical settings, but in smaller populations which showed a numerically higher overall incidence rate of haemostasis within 10 minutes. The phase II studies had the limitation that they were not powered for efficacy assessment. The main efficacy variable and the statistical methods were in accordance with the respective guidelines (CPMP/EWP/2330/99, CPMP/EWP/482/99 and CPMP/BPWG/1089/00). In all these studies thrombin alfa was applied with a gelatine sponge. Overall, thrombin alfa demonstrated robust and consistent efficacy in typical challenging surgical settings.

The company has claimed a good indirect evidence of superiority of Recothrom over placebo. The analysis of placebo data derived from the pivotal 499E01 study, meta-analysis of studies conducted with previously approved in the EU fibrin sealant products allowed to see an overall statistical significance of haemostatic effect at 10 min. However the statistical significance has not been reached in individual surgeries as such comparison was not powered and pre-defined. Nevertheless, the company claims that it provides a sufficient argument for use of bovine thrombin as a comparator and allows to conclude on non-inferiority of Recothrom against bovine thrombin at least in neurosurgery, AV graft and liver surgeries.

Finally the pivotal study 499E01 was double-blinded study of a good quality. It is expected that double-blinded non-inferiority study will provide with more valid results than open label studies based on subjective assessment of haemostatic response.

In a non-controlled clinical study thrombin alfa applied with a spray applicator restored haemostasis in 90% of subjects with burn injury in wound excision sites where necrotic tissue was removed for autologous skin transplantation.

The total study populations did not restrict elderly individuals and patients with hepatic and renal function/disease, and concurrent anticoagulation/anti-platelet therapies and included subjects rather typical for surgical interventions in general. Thrombin alfa topically administered exerts no systemic effects, acts locally, does not circulate in the blood as a free, active molecule, but is rapidly bound to endogenous inhibitors and inactivated.

The safety database of thrombin alfa comprises 583 subjects and is deemed sufficient. Recothrom is well tolerated and exhibited similar adverse event profiles as bovine thrombin in phase III. Similar rates of adverse events, serious adverse events, and deaths were observed between treatment groups in phase III and II studies. Thrombin alfa also demonstrated a superior immunogenicity profile to bovine thrombin, based on a significantly lower incidence of post-treatment anti-product antibody development, i.e. 1.5% vs. 22%. Anti-product antibody development following exposure to bovine thrombin has been linked to development of both bleeding and clotting disorders. The low incidence of antibody development following exposure to thrombin alfa, and following the re-exposure to thrombin alfa in patients who were previously exposed to bovine thrombin, the absence of anti-thrombin neutralising antibodies, and the absence of clinical sequelae in those subjects suggest that rhThrombin use will be less problematic than the use of bovine thrombin.

Thrombotic and immunogenicity risks are well known with use of clotting factors and were previously attributed to fibrin sealants. The immunogenicity risks with use of recombinant human thrombin from provided clinical data appears significantly lower than the risk established with bovine, porcine and human plasma derived products which are associated with TSE and potential viral transmission risks.

As found from the comparison, the efficacy results from 499E01 study seem to be comparable to the haemostatic efficacy found with other previously approved fibrin sealant products both in terms of proportion of respondents and the comparability of the chosen 10 min duration for the primary efficacy endpoint.

The total exposure through 16 April 2009 included at least 166,834 based on the product utilization assumed to equal one unit per patient. No adverse events were reported so far in the USA.

V.2 Risks

The efficacy of Recothrom has not been sufficiently demonstrated as a superiority study against placebo in general internal surgery is generally expected. In addition, the chosen surgical settings are inadequate for the intended indication. The “general haemostasis” claim mainly covers use in parenchymal organs. If a product under this indication would be used in vascular surgery to stop suture line bleeding, this would be off-label use, since for this purpose the product should be labelled with the indication “suture support in vascular surgery”. Special clinical trials demonstrating safe and effective use in this demanding kind of surgery would be required. The same holds for neurosurgery, which is a special indication as well. Efficacy for the intended indication has therefore not been demonstrated. Further, the clinical relevance of TTH differences attained in liver and spinal surgeries was difficult to appreciate. The justification for the conduct of the single-arm study exploring the use of spray applicator in burn surgery is considered to be insufficient to support the licensure of the spray applicator.

It is unclear whether the clinical settings (specialised surgeries – AV graft, PAB surgery and neurosurgery and hepatic resection) utilised in the pivotal study and the totality of the clinical evidence may be sufficient to extrapolate the efficacy in general haemostatic use.

Efficacy in PAB surgery has not been demonstrated and thus should be reflected in the proposed indication. Based on the currently available clinical data the following conclusions can be drawn:

- Thrombin alfa is associated with a very low incidence of post-treatment anti-product antibody formation (range of 0% to 1.6% in the individual studies completed).
- Development of antibodies to thrombin alfa following exposure to the product was not associated with clinical sequelae i.e. adverse or serious adverse events in the studies completed.
- There has been no case of formation of neutralizing antibodies in 543 subjects exposed for which antibody analysis data are available, in phase II and phase III studies including the phase IIIb study.

Therefore, as far as can be assessed after experience in single use only, the immunogenicity risk is considered to be low and it is followed up by the company in the re-exposure study. The incidence of thrombotic events across all studies was balanced between groups of patients.

No significant safety risks from completed clinical studies (including post-marketing studies in the USA) and from post-marketing history of the product in the USA are currently identified with Recothrom.

Any theoretical immunogenicity and thrombogenicity risks are well covered in the RMP.

V.3 Balance

From the CHMP point of view, the use of the haemostatic product with lower immunogenicity, hypersensitivity and thrombotic risks, lacking aprotinin and devoid of associated risks with plasma derived thrombin TSE and viral transmission is well justified. There is a need for haemostatic support in the light of life-threatening risk of bleeding associated with the surgery and limited usefulness of some conventional tools such as ligature, cauterization, laser, sutures etc. in a small, difficult to visualise and identify the source of bleeding target areas (spinal, PAB, AV graft). The immunogenic risks with Recothrom are considerably lower (1.2-1.5%) compared to those with bovine thrombin (up to 18-28%). In addition, the shift of paradigm from using bovine and aprotinin-containing products is considered to be favourable for clinical care of surgical patients. However, it is considered that the efficacy for the intended indication in "general haemostasis" has not been demonstrated based on the data from the pivotal phase III study in the specialised clinical settings (specialised surgeries – AV graft, PAB surgery and neurosurgery and hepatic resection) and supportive phase II studies.

V.4 Conclusions

The B/R balance is considered negative since the efficacy for Recothrom against placebo has not been sufficiently demonstrated.