HAEMOSTATIX LTD

CLINICAL STUDY REPORT

A Controlled, Randomized, Multi-centre, Double Blind, Phase II Study to Evaluate Efficacy and Safety of Topical PeproStat in Intraoperative Surgical Haemostasis

(Short title: CLOTFAST 2)

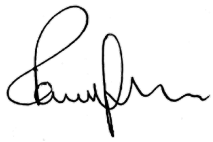
Protocol Number:	HX-02-PEP
Investigational Medicinal Product:	PeproStat™
Indication:	Haemostasis
Phase:	II
Sponsor:	Haemostatix Ltd BioCity Nottingham NG1 1GF United Kingdom
Coordinating Investigator	Paul Hayes, MD Addenbrooke's Cambridge University Hospitals NHS Foundation Trust, Hills Road Cambridge CB2 0QQ United Kingdom
First Patient, First Visit:	31 March 2017
Last Patient, Last Visit:	23 August 2017
Date of Report:	08 March 2018
Report Version:	Version 1.0

The study was conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki and with other applicable regulatory requirements.

REPORT APPROVAL FORM

Trial No.	HX 02 PEP
Trial Title:	A controlled, randomized, multi-centre, double blind, Phase II study to evaluate efficacy and safety of topical PeproStat in intraoperative surgical haemostasis
Sponsor:	Haemostatix Ltd
CSR document ver.:	1.0 dated 08 March 2018

This is to confirm that below undersigned individuals have read this report and confirm that to the best of their knowledge, it accurately describes the conduct and results of the above referenced trial.

Approved by:	**Signature:**	**Date:**
Istvan Zatik Medical Monitor Ergomed		09-Mar-2018
Paul Hayes, MD Coordinating Investigator Addenbrooke's Cambridge University Hospitals NHS Foundation Trust		9th March 2018
Heike Hucke Trial Statistician Ergomed		2018-03-12

2. SYNOPSIS

Name of Company: Haemostatix	**Volume:** (For national authority use only)
Name of Finished Product: PeproStat™	**Page:**
Name of Active Ingredient(s): Recombinant human albumin (rHA)-Mal-PEG12- Glycine-Proline-Arginine-Proline-Glycine	
Title of Study: A Controlled, Randomized, Multi-centre, Double blind, Phase II Study to Evaluate Efficacy and Safety of Topical PeproStat in Intraoperative Surgical Haemostasis (Short title: CLOTFAST 2)	
Protocol Number: HX-02-PEP	
Study Period:	**Study Phase:** II
Date of first patient, first visit: *31 March 2017*	
Date of last patient, last visit: *23 August 2017*	
Coordinating Investigator: Paul Hayes, MD **Other Investigators:** Dr Ibrahim Omerhodžić, Prof. Harun Brkić, MD, Prof.Adi Rifatbegović, MD, Prof. Gordan Galić, MD, Prof. Krešimir Rotim, MD, Prof. Leonardo Patrlj, MD, Mirko Šarlija, MD, Prof. Pawel Słoniewski, MD, Dr hab. Maciej Słupski, Prof. dr hab. n. med. Piotr Gutowski, Prof. Lazar Davidovic, MD, Igor Djurisic, MD, Prof. dr Miroslav Ilic, MD, Dejan Marinkovic, MD, Dr J Vince Smyth	
Study Centre(s): Multi-centre study conducted in Europe at 16 centres.	
Publication(s): None	
Objectives: **Primary:** to evaluate the efficacy of PeproStat in intraoperative haemostasis in adult subjects who underwent liver/soft tissue surgery, vascular surgery or spine surgery. **Secondary:** to further investigate the efficacy and safety of PeproStat in achieving haemostasis in adult subjects who underwent open liver/soft tissue, vascular and spine surgery.	
Study Design: This was a prospective, interventional, randomised, controlled, double-blind, parallel group Phase II study in adult subjects scheduled to undergo liver/soft tissue surgery, vascular surgery or spine surgery. Subjects were randomised in a 2:1 ratio (PeproStat:Saline). Screening phase of up to 28 days, an interventional study period (Day 1), dense monitoring (Day 2), observational monitoring up to discharge (Day 5) and an end-of-study follow-up visit on Day 30±7 days	
Number of Subjects (planned and analysed): 240 subjects planned; 169 subjects analysed	
Diagnosis and Main Criteria for Inclusion: **Screening/baseline** 1. Subject was undergoing a planned open liver/soft tissue, vascular, or spine surgery. 2. Adult males and females ≥18 years of age at screening. **Intraoperative** 3. Subject presented a TBS with mild or moderate bleeding, which standard measures did not control. 4. No other intraoperative complications other than bleeding. 5. No signs of infection or abscess development. 6. TBS with surface area of ≤70 cm^2.	
Test Product, Dose and Mode of Administration, and Lot Number(s): 12.5 mg PeproStat as 5 mL of 2.5 mg/mL solution for local, topical application in a haemostatic gelatin sponge; batch number: HMXP03/P06716.	

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Reference Therapy, Dose and Mode of Administration, and Lot Number(s): 5 mL of physiological Saline (0.9% sodium chloride) for local, topical application in a haemostatic gelatin sponge; batch number: HMXP02/P06616.

Duration of Treatment: During surgery on Day 1 (Visit 3).

Criteria for Evaluation:

Efficacy:

1. Time to haemostasis
2. Number and amount of haemostatic sponge used
3. Use of alternate haemostatic agents at the TBS
4. Investigator efficacy assessment: global score for efficacy to obtain haemostasis and global score for ease of use of study treatment

Safety:

1. Adverse events
2. Clinical laboratory assessments
3. Physical examination
4. Vital signs
5. Pulse oximetry
6. Electrocardiogram
7. Concomitant medications

Statistical Methods:

Efficacy:

The primary endpoint of the study was the efficacy in terms of Time To Haemostasis (TTH) at the primary Target Bleeding Site (TBS), measured in minutes from the start of treatment application (TxStart) at the primary TBS to the achievement of haemostasis at that site or to the end of the 10-minute assessment period if haemostasis has not yet been achieved. If haemostasis was not achieved within 10 minutes, the subject was considered a treatment non-responder.

All obtained data on this endpoint (applied dosages, TTH, failure to achieve haemostasis) were described using descriptive and exploratory statistics. Additionally, the distributions of the parameters were compared between the treatment groups.

For categorical measurements, Fisher's exact test for contingency tables was used, while t-tests were applied to compare the means of (quasi-)continuous measurements. Two-sided 95% CIs for mean differences are presented. As a sensitivity analysis, treatment comparisons were performed with the non-parametric Wilcoxon signed-rank test to study the robustness of the parametric results.

Since the primary endpoint TTH could include censored values (if haemostasis was not achieved within 10 minutes) statistical methods of survival analysis were also applied. This included estimates and tests for the hazard rate and the presentation of Kaplan-Meier curves for the time to haemostasis.

For the subset of subjects who received treatment for a secondary TBS, the analyses described above were repeated for the time to haemostasis at that bleeding site.

To provide a comprehensive overview of the efficacy of the study medication, all of the secondary parameters were analysed using descriptive and exploratory statistics. Also, the distributions of the parameters were compared between the treatment groups.

For categorical measurements, Fisher's exact for contingency tables was used, while t-tests were applied

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to compare the means of (quasi-)continuous measurements. As a sensitivity analysis the mean comparisons were additionally performed with the non-parametric Wilcoxon signed-rank test to assess the robustness of the parametric results.

The analyses of the primary and secondary parameters were performed for the FAS and the PP populations and are presented by surgery type and in total.

Safety:

All analyses were performed for the safety analysis set. Whenever applicable, analyses are presented stratified by surgery type and overall. Adverse events were coded according to version 20 of the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus. Coding was reviewed and approved by a medical expert before database lock.

All TEAEs, related TEAEs (i.e., TEAEs definitely, probably or possibly related to the study medication), and serious TEAEs were summarized and tabulated according to MedDRA system organ class (SOC) and sorted according to the preferred term (PT). Multiple counts within a PT or SOC (repeated or different included terms or changes in descriptors) were counted only once for the calculation of incidences.

Descriptive summary tables per treatment showing the number and percent of subjects with a TEAE and the total number of TEAEs were generated. Any TEAEs leading to withdrawal or death were listed.

Global incidences of primary SOC and PT were calculated for

- All TEAE irrespective of the causality assessment.
- All related TEAEs (definitely, probably or possibly related).
- All TEAEs by worst severity.
- All serious TEAEs.

The indicated frequency tables will be presented by treatment arm.

A listing of special cases containing subject identification, age, sex, TEAE descriptors was prepared for the following types of TEAEs:

- SAE.s
- TEAEs which led to death
- TEAEs which led to discontinuation

For vital signs, descriptive analyses of values and their changes to baseline are presented by treatment and time point.

For each of the ECG parameters descriptive statistics per scheduled time point and the changes from baseline are presented by treatment arm. Frequency tables show the overall interpretation of the Investigator for each time point and treatment arm. Additionally, QTc was calculated according to the Fridericia and Bazett corrections.

Time profiles of safety laboratory parameters were analysed by presenting sampling statistics for the values at each time point as well as their differences to baseline per treatment arm. Laboratory values outside the normal range were listed and flagged. The corresponding normal ranges were included. Descriptive statistics for each lab test at the scheduled time and their changes to baseline for quantitative laboratory parameters are presented. For semi-quantitative urinalysis results frequency tables are presented.

Analysis of the immunogenicity testing for the safety analysis set present estimates of the incidence of antibody development to PeproStat at the end of the trial including 95% CIs.

Efficacy Results:

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- At the primary target bleeding site, for all surgeries, the mean (SD) TTH was lower in the PeproStat group (4.3 [3.01] minutes) than in the Saline group (5.7 [3.47] minutes). Statistically significant differences between PeproStat and Saline (in favour of PeproStat) were seen for all surgeries ($p = 0.0085$ [t-test] and $p = 0.0137$ [Wilcoxon sign-rank test]) and for spine surgery ($p = 0.0222$ [t-test] and $p = 0.0268$ [Wilcoxon sign-rank test]).
    - A total of 15 subjects received treatment at a secondary TBS: 11 subjects who underwent open liver/soft tissue surgery and 4 subjects who underwent vascular surgery. Time to haemostasis for the FAS was similar to that seen for the primary TBS: overall, subjects achieved haemostasis within 5 minutes. No statistically significant differences were seen for all surgeries, or by surgery type.
- Overall, for all surgeries, the majority of subjects (115/169 subjects [68.0%]) achieved haemostasis within 5 minutes. While the majority of subjects in each treatment group had achieved haemostasis within 5 minutes, more subjects treated with PeproStat (84/114 subjects [73.7%]) achieved haemostasis within 5 minutes than did subjects who were treated with Saline (31/55 subjects [56.4%]).
- For all surgeries, median time to haemostasis for subjects treated withPeproStat was 3.0 minutes and for subjects treated with Saline was 5.0 minutes. Median time to haemostasis for subjects treated with PeproStat ranged from 2.5 minutes to 5.0 minutes depending upon surgery type: median time to haemostasis was shortest in PeproStat subjects who had vascular surgery (2.5 minutes) and longest in subjects who underwent open liver/soft tissue surgery (5.0 minutes).
- No subjects in the study had re-bleedings at the primary TBS after haemostasis within 10 minute observation period.
- For all surgeries, overall, 88.76% of subjects (150/169 subjects) in the FAS met the definition of responder for the primary TBS. More responders were seen in subjects treated with PeproStat (91.23% [104/114 subjects]) than those treated with Saline (83.64% [46/55 subjects]).
- For all surgeries, overall, 7 subjects' procedures required the application of a second sponge for the primary TBS (FAS): 6 subjects treated with PeproStat and 1 subject treated with Saline. Six of those 7 subjects who required the application of a second sponge had open liver/soft tissue surgery (5 subjects treated with PeproStat and 1 subject treated with Saline); the other had spine surgery (1 subject treated with PeproStat).
- For all surgeries, overall, 32.54% of the procedures used 0 to 25% of the first sponge and 31.36% of procedures used 76 to 100% of the first sponge for the primary TBS. Less than 20% of all surgeries used 26 to 50% of the sponge and less than 20% of all surgeries used 51 to 75% of the sponge.
- For all surgeries, overall, the majority of alternative methods for the primary TBS used for non-responders was cautery (63.19% [12/19 subjects) followed by sutures (42.11% [8/19 subjects]), pressure (26.32% [5/19 subjects]), other (21.05% [4/19 subjects), and alternative haemostatic agents (15.79% [2/19 subjects]).
- Overall, 62.3% of Investigators (71/114 Investigators) rated the efficacy of PeproStat to obtain haemostasis as excellent or very good compared with 45.5% of Investigators (25/55 Investigators) rating the efficacy of Saline to obtain haemostasis as excellent or very

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good.

- Ease of use of the study treatment was ranked from 1 (very difficult) to 5 (very easy). For all surgeries, overall, the majority of Investigators ranked both the PeproStat and Saline as a 4 or 5 (93.5% [158/169 Investigators]).
- For all surgeries, the mean (SD) time to final haemostasis was lower in the PeproStat group (4.8 [4.38] minutes) than in the Saline group (6.2 [4.37] minutes) for the FAS; results for the PP population were similar.

Post-Hoc Results:

- Subgroup analysis for subjects with mild bleeding:
  - Overall, for all surgeries with mild bleeding, the mean (SD) TTH was shorter in the PeproStat group (3.2 [2.10] minutes) than in the Saline group (5.9 [3.57] minutes) for the FAS. In comparison, for all surgeries and all subjects, the mean (SD) TTH was 4.3 (3.01) minutes (PeproStat group) and 5.7 (3.47) minutes (Saline group) for the FAS.
  - The mean (SD) TTH was shorter in the PeproStat group for subjects with mild bleeding who had open liver/soft tissue surgery, (3.2 [1.54] minutes for PeproStat versus 5.8 [3.67] minutes for Saline), vascular surgery (3.3 [2.40] minutes for PeproStat versus 5.6 [3.73] minutes for Saline), and spine surgery (3.1 [2.16] minutes for PeproStat versus 7.0 [3.56] minutes for Saline). Statistically significant differences in mean time – in favour of PeproStat – were observed for each) surgery type.
  - Results for the PP population were similar to those seen in the FAS.
  - Overall, for all surgeries with mild bleeding for all time points, the cumulative percentages of subjects achieving haemostasis was higher in subjects in the PeproStat group compared with the Saline group for the FAS. For example, after 5 minutes, 87.2% of subjects in the PeproStat group had achieved haemostasis compared with 50.0% of subjects in the Saline group and after 7 minutes, 97.9% of subjects in the PeproStat group had achieved haemostasis compared with 65.4% in the Saline group. In comparison, for all surgeries and all subjects, for all time points, the cumulative percentage of subjects in the FAS who achieved haemostasis, after 5 minutes, was 73.7% (PeproStat group) and 56.4% (Saline group), and at 7 minutes was 85.1% (PeproStat group) and 67.3% (Saline group).

Safety Results:

- Overall, 33.7% of subjects (57/169 subjects) experienced 103 TEAEs:
  - PeproStat: 35.4% of subjects (40/113 subjects) experienced 72 TEAEs.
  - Saline: 30.4% of subjects (17/56 subjects) experienced 31 TEAEs.
  - The only TEAE that occurred in ≥5% of subjects for any treatment was anaemia 8.3%, 14/169 subjects:
    - PeproStat: 9.7% of subjects (11/113).
    - Saline: 5.4% of subjects (3/56).

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- Overall, 7.1% of subjects (12/169 subjects) experienced 13 SAEs:
    - PeproStat: 8.0% of subjects (9/113).
    - Saline: 5.4% of subjects (3/56).

  Duodenal ulcer haemorrhage was the only AE of special interest considered serious, experienced by a subject who underwent vascular surgery and received PeproStat; the AE was not considered related to the study procedure, or the treatment received.
- Overall, only 2 TEAEs were considered treatment related (C-reactive protein increased and procedural haemorrhage), which were experienced by 2 subjects (1.2%, 2/169 subjects) who both underwent spine surgery and were treated with PeproStat. However, it should be noted that despite being considered as possibly related to the study medication the haemorrhage occurred during surgery and that the subject that experienced a TEAE of procedural haemorrhage did not experience re-bleeding after application of study medication, or need re-surgery at the TBS.
- Overall, the majority of TEAEs were mild or moderate in intensity: only 2.4% of subjects (4/169) experienced a TEAE that was severe in intensity and all were considered SAEs.
- Overall, 15.4% of subjects (26/169 subjects) experienced 34 TEAEs of special interest, of which the following occurred in more than one subject:
    - Anaemia: 7.1%, (8/113) (PeproStat) and 3.6%, (2/56) (Saline).
    - Blood count abnormal: 5.3%, (6/113) (PeproStat).
    - Haematocrit decreased: 3.6%, (2/56) (Saline).
    - Procedural haemorrhage: 4.4%, (5/113) (PeproStat) and 3.6%, (2/56) (Saline). However, for the subjects who experienced a TEAE of procedural haemorrhage, it should be noted that the haemorrhages occurred during surgery and that the subjects did not experience re-bleeding after application of study medication, or need re-surgery at the TBS.
- Only one TEAE led to discontinuation: the SAE of pulmonary embolism that led to the death of a subject who underwent open liver/soft tissue surgery and received PeproStat. The SAE occurred 5 days after administration of the study medication and the study procedure, and was, therefore, not considered related to either the study medication or the study procedure.
- Mean changes from baseline in clinical laboratory tests were small and not clinically meaningful. No subjects were discontinued from the study for abnormal laboratory values.
- There were no safety concerns from physical examination findings, vital signs, or ECG findings.

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Conclusions:

- Since mean TTH was statistically significantly lower in the PeproStat group than in the Saline group, PeproStat was efficacious in the treatment of haemostasis.
- PeproStat was more efficacious than Saline in the treatment of haemostasis when assessed by achieving haemostasis for all surgeries in under 5 minutes, median time to haemostasis for vascular and spine surgery, and time to final haemostasis.
- PeproStat's (5 mL of 2.5 mg/mL) effect was more pronounced for subjects that presented mild bleeding.
- The use of PeproStat was safe and generally well tolerated.
- PeproStat is a first in class topical haemostat with a novel mode of action, which does not require thrombin for clot formation. Analysis by surgery type compared to baseline heparin usage suggests that PeproStat demonstrates efficacy as a haemostatic agent in highly heparinised subjects (vascular surgery) as well as in subjects receiving prophylactic or no heparin (liver/soft tissue and spine surgery), which would merit further investigation.
- PeproStat applied by gelatinous sponge has been shown to be an effective haemostatic treatment for a wide variety of surgery types and for subjects receiving diverse anti thrombotic medications, including heparin.

Date of Report, version: Version 1.0