CSL Behring

RESULT SUMMARY

Efficacy and safety of Haemocomplettan® P in patients experiencing acute bleeding while undergoing aortic-replacement surgery

BI3023_2002

Investigational product:	Haemocomplettan® P; fibrinogen concentrate, human (FCH)
Indication studied:	Therapeutic use of FCH in acute bleeding during aortic repair surgery
Phase:	II
Design:	Single-center, prospective, randomized, stratified, double-blind, placebo-controlled, parallel-group
Study dates:	First subject in: 19 June 2008 Last subject out: 21 April 2010
Sponsor:	CSL Behring GmbH Emil-von-Behring Strasse 76 35041 Marburg Germany
Report type:	Result Summary (based on Clinical Study Report Version 2.0)
Result summary date:	31 March 2015

The study was performed in compliance with Good Clinical Practice.

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NAME OF COMPANY: CSL Behring GmbH NAME OF FINISHED PRODUCT: Haemocomplettan P; fibrinogen concentrate, human (FCH) NAME OF ACTIVE INGREDIENT(S): Fibrinogen concentrate, human	**INDIVIDUAL STUDY TABLE** REFERRING TO PART - OF THE DOSSIER VOLUME: - PAGE: -	IF REQUIRED: (FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY:

Efficacy and safety of Haemocomplettan P in patients experiencing acute bleeding while undergoing aortic-replacement surgery

INVESTIGATOR(S):

One investigator, Dr Niels Rahe-Meyer, in one country enrolled subjects for the study.

STUDY CENTER(S):

One center in Germany: Medical School Hannover (MHH), Carl-Neuberg-Strasse 1 / K5, 30625 Hannover, Germany.

PUBLICATION (REFERENCE):

There have been 3 publications reporting results from study BI31023_2002.

Solomon C, Hagl C, and Rahe-Meyer N. Time course of haemostatic effects of fibrinogen concentrate administration in aortic surgery. Br J Anaesth. 2013;110(6):947–56.

Rahe-Meyer N, Solomon C, Hanke A, Schmidt DS, Knoerzer D, Hochleitner G, Sørensen B, Hagl C, and Pichlmaier M. Effects of fibrinogen concentrate as first-line therapy during major aortic replacement surgery: a randomized, placebo-controlled trial. Anesthesiology. 2013;118(1):40-50. Erratum in: Anesthesiology. 2013;118(5):1244.

Rahe-Meyer N1, Hanke A, Schmidt DS, Hagl C, and Pichlmaier M. Fibrinogen concentrate reduces intraoperative bleeding when used as first-line hemostatic therapy during major aortic replacement surgery: results from a randomized, placebo-controlled trial. J Thorac Cardiovasc Surg. 2013;145(3 Suppl):S178-85.

STUDY PERIOD (YEARS): Date of first enrolment: 19 June 2008 Date of last completed: 21 April 2010	PHASE OF DEVELOPMENT: II

OBJECTIVES:

Primary objective

To determine if FCH effectively reduced the amount of allogeneic blood products needed in patients experiencing acute bleeding during aortic-replacement surgery.

Secondary objective

To determine if FCH was safe and well-tolerated in patients experiencing acute bleeding during aortic-replacement surgery.

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METHODOLOGY:

This was a single-center, prospective, randomized, stratified, double-blind, placebo-controlled, parallel-group, Phase II study.

NUMBER OF SUBJECTS (PLANNED AND ANALYZED):

Planned: 30 subjects in each of the 2 study arms, totaling approximately 60 subjects.

Analyzed: 80 subjects were enrolled and 61 subjects were analyzed in the safety set and 60 subjects were analyzed in the modified full analysis set (MFAS).

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

The complete set of **inclusion criteria** were:

- 18 years of age or older.
- Undergoing elective thoracoabdominal aortic aneurysm repair surgery (TAAA) or thoracic aortic aneurysm repair surgery (TAA).
- Understood and willingly gave written informed consent to participate following an explanation of study background, restrictions, and procedures.
- Experienced clinically relevant bleeding of the microvasculature (defined as a 5-minute bleeding mass of 60 to 250 g) following removal of cardiopulmonary bypass (CPB) during surgery.
- Intra-operative conditions prior to administration of study medication:
  - Body temperature > 36°C.
  - Blood pH > 7.3.
  - Hemoglobin > 8.5 g/dL.
  - Activated coagulation time (ACT) < 150 seconds.

In addition, **key exclusion criteria** included:

- Previous aortic repair at the same aortic site (redo surgery).
- Undergoing an emergency operation (i.e. the required surgery for TAA or TAAA was not elective).
- Proof or suspicion of a congenital or acquired coagulation disorder (e.g. von Willebrand disease or via severe liver disease).
- Myocardial infarction (MI) or apoplexy in the 2 months preceding study surgery.
- Acetylsalicylic acid (ASA) administration in the 3 days preceding study surgery, and a pathological (< 74.5 U) arachidonic acid (ASPI) Multiplate® test immediately preceding the start of surgery.

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- Clopidogrel administration in the 5 days preceding study surgery, and a pathological (< 31.1 U) adenosine diphosphate/prostaglandins (ADP/PG) Multiplate test immediately preceding the start of surgery.
- Tirofiban administration in the 2 days preceding study surgery, and a pathological (< 94.1 U) thrombin receptor activating peptide (TRAP) Multiplate test immediately preceding the start of surgery.
- Phenprocoumon administration in the 5 days preceding study surgery, and an international normalized ratio (INR) > 1.28 immediately preceding the start of surgery.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NO.

FCH is a lyophilizate that was dissolved in 50 mL water for injection resulting in an intravenous infusion of 20 mg/ml.

Dosing was individually determined based upon the maximum clot firmness (MCF) (measured by fibrinogen thromboelastometry [FibTEM®]) and body weight (b.w.): (22 [mm] − MCF [mm]) * b.w. [kg] / 140 [m] = whole g fibrinogen to be dosed as FCH.

Batch No. used in this study:

007 680 11A, 045 680 11A, 101 680 11E

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NO.

Placebo, in the form of a solution for injection of 0.9% saline, was used as the reference therapy in this study. The placebo was administered according to the same conditions and with equivalent volume to that of the FCH doses described above.

Batch No. used in this study:

8331A241, 8414B13, 8441A191, 8511A191, 9062A242

Manufacturer: B.Braun, Melsungen, Germany

DURATION OF TREATMENT:

FCH or placebo were administered as a single intravenous infusion over approximately 10 minutes after the first clinically relevant bleeding following removal of the subject from CPB.

CRITERIA FOR EVALUATION:

Efficacy:

Primary efficacy endpoint

Combined number of units of allogeneic blood products (platelets, fresh frozen plasma [FFP], and/or red blood cells [RBCs]) administered to subjects between administration of study medication and 24 hours thereafter.

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Secondary efficacy endpoints

- Number of units (not combined) for each of platelets, FFP, and RBCs administered to subjects between administration of study medication and 24 hours thereafter.
- Proportion of subjects that received no allogeneic blood products (neither platelets, FFP nor RBCs) between administration of study medication and 24 hours thereafter.
- Difference in quantity of blood loss (5-minute bleeding mass) from approximately 15 minutes before to approximately 15 minutes after administration of study medication.
- Quantity of blood loss (30-minute blood drainage volume) between last suture and 24 hours after administration of study medication.
- Duration of ventilation.
- Duration of stay in intensive care unit (ICU) following last suture of initial surgery.
- Duration of hospital stay following last suture of initial surgery.
- Proportion of subjects that received a follow-on surgery to correct unacceptable bleeding within 5 days of last suture.
- Mortality at 45 days post-surgery.

Additional efficacy variables

- Rotation thromboelastometry (ROTEM) assays, including MCF via FibTEM.
- Fibrinogen levels.
- Other coagulation parameters.
- Multiplate measurements on platelet function and antiplatelet therapy.

Safety

- Adverse events (AEs), including those of special interest, i.e. signs of kidney failure, cross-sectional paralysis (e.g. paraplegia), allergic reactions, MI, and thromboembolism.
- Physical examination and vital signs.
- Hematology.
- Biochemistry.
- Virus safety.

Other variables

- Quality of life.

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STATISTICAL METHODS:

Results of a historical experience in a single center showed an average consumption of allogeneic blood products of 16.4 units (U) with a standard deviation (SD) of 7.7 U for TAAA surgery (8.5 ± 5.3 U for TAA surgery).

The aim of this study was to detect a clinically relevant 50% decrease in consumption of allogeneic blood products in the FCH treatment group compared to placebo with a power of more than 80%. Using a 2-sided non-parametric Wilcoxon/Mann Whitney rank sum test a sample size of 30 subjects in each of the 2 treatment groups was required to achieve >80% power to detect a difference of 4.25 U (SD 5.3 U) between the group means at a significance level (alpha) of 0.05. Except for the primary endpoint (24-hours total consumption of blood products), statistical analyses were of descriptive/exploratory nature.

SUMMARY - CONCLUSIONS

Efficacy results:

Assessment of efficacy demonstrated that FCH was more effective than placebo at controlling microvascular bleeding. This is based on the following analyses of the MFAS population, with consistent findings in the full analysis set (FAS) population:

- A statistically significant difference was obtained for the primary endpoint of this study (the combined number of units of allogeneic blood products [platelets, FFP, and/or RBCs] administered to subjects in the 24 hours after the start of infusion of study medication): FCH subjects received a median of 2.0 units of all allogeneic blood products combined compared to a median of 13.0 units in placebo subjects ($p<0.001$). This difference was seen in all surgery types (TAAA and TAA, both with and without proximal bow arch).
- The FCH group needed fewer units of each of the individual blood products, platelets, FFP, or RBCs, than the placebo group within 24 hours after start of infusion ($p<0.001$).
- Whereas all subjects in the placebo group required allogeneic blood products to control their microvascular bleeding, 44.8% of FCH subjects did not require any allogeneic blood products ($p<0.0001$).
- There was a considerable reduction in the 5-minute bleeding mass from before to after infusion with the study medication in the FCH group, with a median difference of -44.0 g compared to +2.0 g in the placebo group ($p<0.0001$).
- There was no difference between treatment with FCH or placebo on the duration of ventilation, the duration of stay in the intensive care unit or hospital, or on quality of life.
- The dose of FCH used ranged from 3 to 12 g.

Safety results:

Analysis of the safety data did not reveal anything that would suggest a safety concern for the

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use of FCH during TAA and TAAA repair surgery. The key safety findings were as follows:

- The proportion of subjects with reported treatment-emergent adverse events (TEAEs; AEs with onset or worsening after the start of infusion of study medication up to Day 10 after surgery) or serious TEAEs was similar in the 2 treatment (TEAEs: 24 [82.8%] FCH subjects, 27 [84.4%] placebo subjects; serious TEAEs (4 [13.8%] FCH subjects, 4 [12.5%] placebo subjects. The majority of the TEAEs reported were typical for patients undergoing cardiac surgery.
- The most frequently reported TEAEs were pleural effusion (11 [37.9%] FCH subjects, 12 [37.5%] placebo subjects), atrial fibrillation (5 [17.2%] FCH subjects, 6 [18.8%] placebo subjects), psychosis postoperative (4 [13.8%] FCH subjects, 2 [6.3%] placebo subjects), and anaemia (reported as anaemia: 3 [10.3%] FCH subjects, reported as anaemia postoperative: 3 [9.4%] placebo subjects).
- There were 5 deaths reported during the study: 1 (3.4%) FCH subject and 4 (12.5%) placebo subjects.
- Nonfatal serious TEAEs were reported in 4 (13.8%; 5 events) FCH subjects: these were autoimmune thrombocytopenia, cardiac arrest, brain stem ischemia, postoperative psychosis, and impaired healing. There were no nonfatal serious TEAEs reported in the placebo group.
- None of the TEAEs reported in the study were considered to be related to study medication and none of the nonfatal TEAEs led to discontinuation from the study.
- The majority of TEAEs were mild (19 [65.5%] FCH, 20 [62.5%] placebo subjects), or moderate (9 [31.0%] FCH, 11 [34.4%] placebo subjects) in severity. There were only 2 (6.9%) FCH and 6 (18.8%) placebo subjects with severe TEAEs.
- There were no clinically relevant changes in hematology or biochemistry values that were not to be expected as a result of cardiac surgery.
- A total of 3 subjects had abnormal biochemistry values that were considered by the investigator to be clinically significant (elevations of aspartate aminotransferase and alanine aminotransferase: 1 subject [placebo group]; elevation of C reactive protein: 1 subject [placebo group]; elevation of urea: 1 subject [FCH group]). None of these abnormal biochemistry values were considered to be related to study medication.
- Changes in vital signs and physical examination findings were minimal, generally similar in both treatment groups, and were not considered to be clinically relevant.
- Close monitoring of events that might have been of concern for the use of FCH during such cardiac surgeries (i.e. signs of kidney failure, cross-sectional paralysis, allergic reactions, MI, and thromboembolism) did not show a difference between FCH and placebo.

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Conclusions:

The findings of this study demonstrate the ability of FCH to restore hemostasis in the case of clinically relevant microvascular bleeding during TAA and TAAA repair surgery, without compromising the safety of the subject. Compared to placebo, infusion of FCH significantly reduces the need for allogeneic blood products and the 5-minute bleeding mass after removal from CPB. FCH was well tolerated during the study and the safety data did not reveal anything that would suggest a safety concern for the use of FCH during the course of cardiac surgery.

Date of the report: 31 March 2015

RELEVANT PROTOCOL AMENDMENTS:

There were 2 substantial amendments made to the original protocol (version 1.0), details of which are summarized below.

Substantial Amendment No. 1(resulting in Protocol Version 2.0): covered the following changes:

1. The indication was expanded to include subjects undergoing elective TAA surgery. The inclusion criteria were modified accordingly.
2. The clinical study design was changed to a multicenter trial with approximately 4 centers in Europe. Note: no centers other than the original recruited subjects, so the study remained a single-center study.
3. The statistical analysis was changed. A second stratum, i.e. subjects undergoing TAA, was included. Therefore the sample size was increased to 60 subjects. Efficacy and safety endpoints remained unaltered.
4. The exclusion criteria were modified to exclude subjects with redos of aortic surgery at the same surgical site.
5. The list of personnel (Appendix 1 of the Clinical Study Protocol) was updated

Substantial Amendment No. 2 (resulting in Protocol Version 3.0), covered the following changes:

1. The interim analysis originally planned to enable the calculation of a sample size for further studies, was removed from the study protocol as there was no longer any intention to run other studies in parallel with this study.
2. The CRO for statistics and data management changed.