Clinical trial results:
REPLACE (Randomized evaluation of fibrinogen versus placebo in complex cardiovascular surgery): a prospective, multinational, multicenter, randomized, double-blind, placebo-controlled, phase III study for the use of Fibrinogen Concentrate (Human) (FCH) in complex cardiovascular surgery

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2011-002685-20
Trial protocol	DE GB FI IT AT CZ PL DK
Global end of trial date	11 September 2014

Results information

Result version number	v1 (current)
This version publication date	29 July 2016
First version publication date	29 July 2016

Trial information

Trial identification

Sponsor protocol code	BI3023_3002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01475669
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CSL Behring GmbH
Sponsor organisation address	Emil-von-Behring-Strasse 76, Marburg, Germany, 35041
Public contact	Trial Registration Co-ordinator, CSL Behring GmbH, clinicaltrials@cslbehring.com
Scientific contact	Trial Registration Co-ordinator, CSL Behring GmbH, clinicaltrials@cslbehring.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 October 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of FCH treatment in controlling microvascular bleeding during complex cardiovascular surgery.

Protection of trial subjects:

This study was carried out in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines, and standard operating procedures for clinical research and development at CSL Behring. The study protocol and all amendments, the Subject Information Sheet, and the Informed Consent Form were reviewed and approved by the independent ethics committee / and Institutional Review Boards of the participating centers.
Before undergoing screening procedures for possible enrollment into the study, subjects were informed, in an understandable form, about the nature, scope, and possible consequences of the study. The investigator was responsible for obtaining a subject's written informed consent to participate in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 January 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	United Kingdom: 24
Country: Number of subjects enrolled	Austria: 5
Country: Number of subjects enrolled	Czech Republic: 19
Country: Number of subjects enrolled	Denmark: 6
Country: Number of subjects enrolled	Finland: 12
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Canada: 21
Country: Number of subjects enrolled	Japan: 48
Worldwide total number of subjects	152
EEA total number of subjects	83

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	72
From 65 to 84 years	77
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

This multinational study enrolled subjects undergoing elective open surgical procedures on any part of the aorta requiring cardiopulmonary bypass. Subjects were enrolled at 34 sites in 11 countries.

Pre-assignment

Screening details:

Screening took place up to 4 weeks before administration of IMP. A total of 579 patients provided written informed consent and 519 eligible subjects were randomized at the start of surgery. Of the 519 randomized subjects, 152 (29.3%) met all intraoperative eligibility criteria and were treated with IMP (FCH arm: n = 78; placebo arm: n = 74).

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	FCH arm

Arm description:

Subjects were administered fibrinogen concentrate, human (FCH).

Arm type	Experimental
Investigational medicinal product name	Fibrinogen concentrate, human
Investigational medicinal product code	FCH
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects who met the the intraoperative eligibility criteria were to receive a single intravenous dose within 5 minutes of the completion of the measurement of the 5-minute bleeding mass. The FCH dose was determined individually based on the maximum clot firmness measured 20 to 30 minutes prior to discontinuation of cardiopulmonary bypass and subject body weight.

Arm title	Placebo arm

Arm description:

Subjects were administered placebo (0.9% sodium chloride solution).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	0.9% sodium chloride solution
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Single dose of 0.9% sodium chloride solution infused intravenously within 5 minutes at a volume equivalent to that needed for FCH.

Number of subjects in period 1	FCH arm	Placebo arm
Started	78	74
Completed	74	68
Not completed	4	6
Adverse event, serious fatal	1	5
Consent withdrawn by subject	1	-
Surgical intervention due to bleeding	-	1
Adverse event, non-fatal	1	-
Moved to another facility, too unwell to complete	1	-

Baseline characteristics

Reporting groups	
Reporting group title	FCH arm
Reporting group description:	
Subjects were administered fibrinogen concentrate, human (FCH).	
Reporting group title	Placebo arm
Reporting group description:	
Subjects were administered placebo (0.9% sodium chloride solution).	

Reporting group values	FCH arm	Placebo arm	Total
Number of subjects	78	74	152
Age categorical Units: Subjects			
< 65 years	38	34	72
>= 65 years	40	40	80
Age continuous Units: years			
arithmetic mean	63.9	64.2	
standard deviation	± 12.96	± 13.53	-
Gender categorical Units: Subjects			
Female	18	23	41
Male	60	51	111
Surgical stratum Units: Subjects			
Primary procedure	71	70	141
Reoperation	7	4	11
Surgery type Units: Subjects			
Thoracic aortic aneurysm repair with proximal arch	32	36	68
Thoracic aortic aneurysm repair, no proximal arch	43	34	77
Thoracoabdominal aortic aneurysm repair	3	4	7
First 5-minute bleeding mass			
First 5-minute bleeding mass:the difference in weight of surgical swabs after 5 minutes of surgical packing of the aortic surgical site			
Units: gram			
median	107	91	
full range (min-max)	60 to 242	60 to 233	-

End points

End points reporting groups

Reporting group title	FCH arm
Reporting group description:	
Subjects were administered fibrinogen concentrate, human (FCH).	
Reporting group title	Placebo arm
Reporting group description:	
Subjects were administered placebo (0.9% sodium chloride solution).	
Subject analysis set title	FCH - ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The intention-to treat (ITT) population (all randomized subjects who received any quantity of investigational medicinal product [IMP]) who were treated with FCH.	
Subject analysis set title	Placebo - ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT population (all randomized subjects who received any quantity of IMP) who were treated with placebo.	
Subject analysis set title	FCH - PP
Subject analysis set type	Per protocol
Subject analysis set description:	
The per-protocol (PP) population (all subjects in the ITT population, excluding subjects who had at least 1 major protocol deviation), who were treated with FCH.	
Subject analysis set title	Placebo - PP
Subject analysis set type	Per protocol
Subject analysis set description:	
The PP population (all subjects in the ITT population, excluding subjects who had at least 1 major protocol deviation), who were treated with placebo.	

Primary: Total units of allogeneic blood products

End point title	Total units of allogeneic blood products
End point description:	
Number of units administered of all allogeneic blood products combined (fresh frozen plasma [FFP], platelets, and red blood cells [RBCs]).	
End point type	Primary
End point timeframe:	
Up to 24 hours after IMP administration	

End point values	FCH - ITT	Placebo - ITT	FCH - PP	Placebo - PP
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	78	74	60	64
Units: units				
median (full range (min-max))	5 (0 to 72)	3 (0 to 25)	5 (0 to 72)	3.5 (0 to 25)

Statistical analyses

Statistical analysis title	FCH arm vs Placebo arm - ITT population
Comparison groups	FCH - ITT v Placebo - ITT
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.026 [1]
Method	van Elteren test

Notes:

[1] - P value of van Elteren test (stratification by pooled study center).

Statistical analysis title	FCH arm vs Placebo arm - PP population
Comparison groups	FCH - PP v Placebo - PP
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.15 [2]
Method	van Elteren test

Notes:

[2] - P value of van Elteren test (stratification by pooled study center).

Secondary: Total avoidance of allogeneic blood transfusions

End point title	Total avoidance of allogeneic blood transfusions

End point description:

Number of subjects who are alive and do not have any administration of platelets, FFP, and RBCs during the first 24 hours after administration of IMP

End point type	Secondary

End point timeframe:

During the 24 hours after IMP administration

End point values	FCH - ITT	Placebo - ITT	FCH - PP	Placebo - PP
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	78	74	60	64
Units: subjects	12	21	9	19

Statistical analyses

Statistical analysis title	FCH arm vs Placebo arm - ITT population
Comparison groups	FCH - ITT v Placebo - ITT
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.047 [3]
Method	Cochran-Mantel-Haenszel

Notes:
[3] - Cochran-Mantel-Haenszel (CMH) test, stratified by pooled center

Statistical analysis title	FCH arm vs Placebo arm - PP population
Comparison groups	FCH - PP v Placebo - PP
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.058 [4]
Method	Cochran-Mantel-Haenszel

Notes:
[4] - Cochran-Mantel-Haenszel (CMH) test, stratified by pooled center

Secondary: Quantity of blood loss	
End point title	Quantity of blood loss
End point description: Blood drainage volume from the chest	
End point type	Secondary
End point timeframe: At 6, 12 and 24 hours after skin closure	

End point values	FCH - ITT	Placebo - ITT	FCH - PP	Placebo - PP
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	76	74	59	64
Units: mL				
median (full range (min-max))				
6 hours after skin closure	260 (51 to 3125)	297.5 (75 to 1340)	255 (51 to 3125)	297.5 (75 to 1340)
12 hours after skin closure	405 (101 to 3740)	447.5 (140 to 1680)	352 (101 to 3740)	443 (140 to 1680)
24 hours after skin closure	590 (170 to 4420)	682.5 (195 to 2115)	590 (176 to 4420)	695 (195 to 2115)

Statistical analyses

Statistical analysis title	FCH arm vs Placebo arm - ITT population, 6 hours
Comparison groups	Placebo - ITT v FCH - ITT
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.241 [5]
Method	van Elteren test

Notes:
[5] - P-value of van Elteren test, stratified by pooled center

Statistical analysis title	FCH arm vs Placebo arm - ITT population, 12 hours
Comparison groups	Placebo - ITT v FCH - ITT
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.137 [6]
Method	van Elteren test

Notes:

[6] - P-value of van Elteren test, stratified by pooled center

Statistical analysis title	FCH arm vs Placebo arm - ITT population, 24 hours
Comparison groups	FCH - ITT v Placebo - ITT
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.12 [7]
Method	van Elteren test

Notes:

[7] - P-value of van Elteren test, stratified by pooled center

Statistical analysis title	FCH arm vs Placebo arm - PP population, 6 hours
Comparison groups	FCH - PP v Placebo - PP
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.106 [8]
Method	van Elteren test

Notes:

[8] - P-value of van Elteren test, stratified by pooled center

Statistical analysis title	FCH arm vs Placebo arm - PP population, 12 hours
Comparison groups	FCH - PP v Placebo - PP
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.075 [9]
Method	van Elteren test

Notes:

[9] - P-value of van Elteren test, stratified by pooled center

Statistical analysis title	FCH arm vs Placebo arm - PP population, 24 hours
Comparison groups	FCH - PP v Placebo - PP
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.103 [10]
Method	van Elteren test

Notes:

[10] - P-value of van Elteren test, stratified by pooled center

Secondary: Change in bleeding mass

End point title	Change in bleeding mass

End point description:

The 5-minute bleeding mass is measured as the difference in weight of surgical swabs after 5 minutes of surgical packing of the aortic surgical site immediately before and 5 minutes after completion of IMP administration.

End point type	Secondary

End point timeframe:

Immediately before and 5 minutes after completion of IMP administration

End point values	FCH - ITT	Placebo - ITT	FCH - PP	Placebo - PP
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	77	74	59	64
Units: grams				
median (full range (min-max))	-20 (-153 to 40)	-19.5 (-174 to 97)	-19 (-153 to 40)	-18.5 (-126 to 97)

Statistical analyses

Statistical analysis title	FCH arm vs Placebo arm - ITT population
Comparison groups	FCH - ITT v Placebo - ITT
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.319 [11]
Method	van Elteren test

Notes:

[11] - P-value of van Elteren test, stratified by pooled center

Statistical analysis title	FCH arm vs Placebo arm - PP population
Comparison groups	FCH - PP v Placebo - PP
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.23 [12]
Method	van Elteren test

Notes:

[12] - P-value of van Elteren test, stratified by pooled center

Secondary: Mortality

End point title	Mortality

End point description:

Mortality with adjudicated cause of death (thrombotic/thromboembolic event [TEE] or non-TEE event) during the first 24 hours after administration of IMP, and up to 10 days and 30 days after surgery.

End point type	Secondary

End point timeframe:

Within 24 hours after IMP administration, up to 10 days after surgery, and up to 30 days after surgery

End point values	FCH arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	74		
Units: subjects				
Overall, within 24 hours after IMP	0	0		
TEE, within 24 hours after IMP	0	0		
Non-TEE, within 24 hours after IMP	0	0		
Overall, up to 10 days after surgery	1	1		
TEE, up to 10 days after surgery	1	1		
Non-TEE, up to 10 days after surgery	0	0		
Overall, up to 30 days after surgery	1	4		
TEE, up to 30 days after surgery	1	2		
Non-TEE, up to 30 days after surgery	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of blood products

End point title	Consumption of blood products

End point description:

Consumption of each individual blood product administered (FFP, platelets, and RBCs).

End point type	Secondary

End point timeframe:

Up to 24 hours, and up to 10 days after IMP administration

End point values	FCH - ITT	Placebo - ITT	FCH - PP	Placebo - PP
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	78	74	60	64
Units: units				
median (full range (min-max))				
FFP, within 24 hours after IMP administration	4 (0 to 28)	0 (0 to 14)	4 (0 to 28)	0 (0 to 14)
Platelets within 24 hours after IMP administration	1 (0 to 16)	1 (0 to 6)	1 (0 to 16)	1 (0 to 6)
RBCs, within 24 hours after IMP administration	1 (0 to 28)	0 (0 to 6)	1 (0 to 28)	0 (0 to 6)

FFP, up to 10 days after IMP administration	4 (0 to 31)	0 (0 to 14)	4 (0 to 31)	0 (0 to 14)
Platelets, up to 10 days after IMP administration	1 (0 to 23)	1 (0 to 6)	1 (0 to 23)	1 (0 to 6)
RBCs, up to 10 days after IMP administration	2 (0 to 33)	2 (0 to 10)	2 (0 to 33)	1.5 (0 to 8)

Statistical analyses

Statistical analysis title	FCH vs Placebo, ITT population, FFP, 24 hours
Comparison groups	FCH - ITT v Placebo - ITT
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.017 [13]
Method	van Elteren test

Notes:

[13] - P-value of van Elteren test, stratified by pooled center

Statistical analysis title	FCH vs Placebo, ITT population, FFP, 10 days
Comparison groups	FCH - ITT v Placebo - ITT
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.021 [14]
Method	van Elteren test

Notes:

[14] - P-value of van Elteren test, stratified by pooled center

Statistical analysis title	FCH vs Placebo, PP population, FFP, 24 hours
Comparison groups	FCH - PP v Placebo - PP
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.114 [15]
Method	van Elteren test

Notes:

[15] - P-value of van Elteren test, stratified by pooled center

Statistical analysis title	FCH vs Placebo, PP population, FFP, 10 days
Comparison groups	FCH - PP v Placebo - PP
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.137 [16]
Method	van Elteren test

Notes:
[16] - P-value of van Elteren test, stratified by pooled center

Statistical analysis title	FCH vs Placebo, ITT population, platelets, 24 hour
Comparison groups	FCH - ITT v Placebo - ITT
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.089 [17]
Method	van Elteren test

Notes:
[17] - P-value of van Elteren test, stratified by pooled center

Statistical analysis title	FCH vs Placebo, ITT population, platelets, 10 days
Comparison groups	FCH - ITT v Placebo - ITT
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.126 [18]
Method	van Elteren test

Notes:
[18] - P-value of van Elteren test, stratified by pooled center

Statistical analysis title	FCH vs Placebo, PP population, platelets, 24 hours
Comparison groups	FCH - PP v Placebo - PP
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.232 [19]
Method	van Elteren test

Notes:
[19] - P-value of van Elteren test, stratified by pooled center

Statistical analysis title	FCH vs Placebo, PP population, platelets, 10 days
Comparison groups	FCH - PP v Placebo - PP
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.266 [20]
Method	van Elteren test

Notes:
[20] - P-value of van Elteren test, stratified by pooled center

Statistical analysis title	FCH vs Placebo, ITT population, RBCs, 24 hours
Comparison groups	FCH - ITT v Placebo - ITT

Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.101 [21]
Method	van Elteren test

Notes:

[21] - P-value of van Elteren test, stratified by pooled center

Statistical analysis title	FCH vs Placebo, ITT population, RBCs, 10 days
Comparison groups	FCH - ITT v Placebo - ITT
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.553 [22]
Method	van Elteren test

Notes:

[22] - P-value of van Elteren test, stratified by pooled center

Statistical analysis title	FCH vs Placebo, PP population, RBCs, 24 hours
Comparison groups	FCH - PP v Placebo - PP
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.354 [23]
Method	van Elteren test

Notes:

[23] - P-value of van Elteren test, stratified by pooled center

Statistical analysis title	FCH vs Placebo, PP population, RBCs, 10 days
Comparison groups	FCH - PP v Placebo - PP
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.93 [24]
Method	van Elteren test

Notes:

[24] - P-value of van Elteren test, stratified by pooled center

Secondary: Total units of all allogeneic blood products

End point title	Total units of all allogeneic blood products

End point description:

Number of units of all allogeneic blood products combined (FFP, platelets, and/or RBCs) administered during the first 6 hours after administration of IMP, and during 12 hours after administration of IMP.

End point type	Secondary

End point timeframe:

During the 6 hours and 12 hours after IMP administration

End point values	FCH - ITT	Placebo - ITT	FCH - PP	Placebo - PP
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	78	74	60	64
Units: units				
median (full range (min-max))				
6 hours after IMP administration	5 (0 to 67)	3 (0 to 24)	4.5 (0 to 67)	2.5 (0 to 24)
12 hours after IMP administration	5 (0 to 69)	3 (0 to 24)	5 (0 to 69)	3.5 (0 to 24)

Statistical analyses

Statistical analysis title	FCH vs Placebo, ITT population, 6 hours
Comparison groups	FCH - ITT v Placebo - ITT
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.052 [25]
Method	van Elteren test

Notes:

[25] - P-value of van Elteren test, stratified by pooled center

Statistical analysis title	FCH vs Placebo, PP population, 6 hours
Comparison groups	FCH - PP v Placebo - PP
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.147 [26]
Method	van Elteren test

Notes:

[26] - P-value of van Elteren test, stratified by pooled center

Statistical analysis title	FCH vs Placebo, ITT population, 12 hours
Comparison groups	FCH - ITT v Placebo - ITT
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.037 [27]
Method	van Elteren test

Notes:

[27] - P-value of van Elteren test, stratified by pooled center

Statistical analysis title	FCH vs Placebo, PP population, 12 hours
Comparison groups	FCH - PP v Placebo - PP

Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.149 [28]
Method	van Elteren test

Notes:

[28] - P-value of van Elteren test, stratified by pooled center

Secondary: Volume of all allogeneic blood products

End point title	Volume of all allogeneic blood products

End point description:

Volume of all allogeneic blood products combined (FFP, platelets, and/or RBCs) administered during the first 6, 12, and 24 hours after administration of IMP

End point type	Secondary

End point timeframe:

During the 6, 12, and 24 hours after administration of IMP

End point values	FCH - ITT	Placebo - ITT	FCH - PP	Placebo - PP
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	78	74	60	64
Units: mL				
median (full range (min-max))				
6 hours after IMP administration	1120 (0 to 20050)	787.5 (0 to 6500)	1105 (0 to 20050)	715 (0 to 6500)
12 hours after IMP administration	1190 (0 to 20650)	800 (0 to 6500)	1120 (0 to 20650)	800 (0 to 6500)
24 hours after IMP administration	1190 (0 to 21550)	850 (0 to 6800)	1120 (0 to 21550)	880 (0 to 6800)

Statistical analyses

Statistical analysis title	FCH vs Placebo, ITT population, 6 hours
Comparison groups	FCH - ITT v Placebo - ITT
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.049 [29]
Method	van Elteren test

Notes:

[29] - P-value of van Elteren test, stratified by pooled center

Statistical analysis title	FCH vs Placebo, PP population, 6 hours
Comparison groups	FCH - PP v Placebo - PP

Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.138 [30]
Method	van Elteren test

Notes:

[30] - P-value of van Elteren test, stratified by pooled center

Statistical analysis title	FCH vs Placebo, ITT population, 12 hours
Comparison groups	FCH - ITT v Placebo - ITT
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.05 [31]
Method	van Elteren test

Notes:

[31] - P-value of van Elteren test, stratified by pooled center

Statistical analysis title	FCH vs Placebo, PP population, 12 hours
Comparison groups	FCH - PP v Placebo - PP
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.163 [32]
Method	van Elteren test

Notes:

[32] - P-value of van Elteren test, stratified by pooled center

Statistical analysis title	FCH vs Placebo, ITT population, 24 hours
Comparison groups	FCH - ITT v Placebo - ITT
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.038 [33]
Method	van Elteren test

Notes:

[33] - P-value of van Elteren test, stratified by pooled center

Statistical analysis title	FCH vs Placebo, PP population, 24 hours
Comparison groups	FCH - PP v Placebo - PP
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.17 [34]
Method	van Elteren test

Notes:

[34] - P-value of van Elteren test, stratified by pooled center

Secondary: Time from administration of study drug to completion of skin closure	
End point title	Time from administration of study drug to completion of skin closure

End point description:

End point type	Secondary

End point timeframe:

Average 2 hours

End point values	FCH - ITT	Placebo - ITT	FCH - PP	Placebo - PP
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	78	74	60	64
Units: minutes				
median (full range (min-max))	84.5 (16 to 329)	77 (20 to 192)	83.5 (16 to 300)	71.5 (20 to 192)

Statistical analyses

Statistical analysis title	FCH arm vs Placebo arm - ITT population
Comparison groups	FCH - ITT v Placebo - ITT
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.19 [35]
Method	van Elteren test

Notes:

[35] - P-value of van Elteren test, stratified by pooled center

Statistical analysis title	FCH arm vs Placebo arm - PP population
Comparison groups	FCH - PP v Placebo - PP
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.263 [36]
Method	van Elteren test

Notes:

[36] - P-value of van Elteren test, stratified by pooled center

Secondary: Observed peak plasma concentration of fibrinogen (Cmax)	
End point title	Observed peak plasma concentration of fibrinogen (Cmax)

End point description:

Fibrinogen levels were determined using the Clauss assay.

End point type	Secondary

End point timeframe:

At the end of IMP administration

End point values	FCH - ITT	Placebo - ITT	FCH - PP	Placebo - PP
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	77	74	60	64
Units: g/L				
median (full range (min-max))	2.41 (0.47 to 3.7)	1.105 (0.31 to 2.23)	2.415 (0.47 to 3.7)	1.12 (0.36 to 2.23)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From screening up to 45 days after the administration of IMP, for subjects who were treated.	
Adverse event reporting additional description:	
The safety population comprised all randomized subjects who received any quantity of IMP. Adverse Event data are treatment-emergent data unless otherwise noted.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups	
Reporting group title	FCH arm
Reporting group description:	
Subjects were administered fibrinogen concentrate, human (FCH).	
Reporting group title	Placebo arm
Reporting group description:	
Subjects were administered placebo (0.9% sodium chloride solution).	

Serious adverse events	FCH arm	Placebo arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 78 (34.62%)	25 / 74 (33.78%)	
number of deaths (all causes)	1	5	
number of deaths resulting from adverse events	0	1	
Vascular disorders			
Haemodynamic instability			
subjects affected / exposed	1 / 78 (1.28%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	2 / 78 (2.56%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphorrhoea			
subjects affected / exposed	0 / 78 (0.00%)	2 / 74 (2.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial haemorrhage			

subjects affected / exposed	0 / 78 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 78 (1.28%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 78 (1.28%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Endotracheal intubation			
subjects affected / exposed	1 / 78 (1.28%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 78 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 78 (1.28%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	1 / 78 (1.28%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			

subjects affected / exposed	2 / 78 (2.56%)	4 / 74 (5.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	5 / 78 (6.41%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	2 / 78 (2.56%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 78 (1.28%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chylothorax			
subjects affected / exposed	1 / 78 (1.28%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 78 (1.28%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mediastinal haemorrhage			
subjects affected / exposed	1 / 78 (1.28%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			

subjects affected / exposed	1 / 78 (1.28%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 78 (1.28%)	2 / 74 (2.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Platelet count decreased			
subjects affected / exposed	2 / 78 (2.56%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 78 (1.28%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Procedural haemorrhage			
subjects affected / exposed	4 / 78 (5.13%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 78 (1.28%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anastomotic haemorrhage			
subjects affected / exposed	1 / 78 (1.28%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endotracheal intubation complication			

subjects affected / exposed	1 / 78 (1.28%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac tamponade			
subjects affected / exposed	1 / 78 (1.28%)	6 / 74 (8.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pericardial effusion			
subjects affected / exposed	2 / 78 (2.56%)	2 / 74 (2.70%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 78 (2.56%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	1 / 78 (1.28%)	2 / 74 (2.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 78 (1.28%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 78 (1.28%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 78 (1.28%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			

subjects affected / exposed	0 / 78 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Low cardiac output syndrome			
subjects affected / exposed	1 / 78 (1.28%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 78 (1.28%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular dysfunction			
subjects affected / exposed	1 / 78 (1.28%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	1 / 78 (1.28%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sick sinus syndrome			
subjects affected / exposed	1 / 78 (1.28%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	1 / 78 (1.28%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	1 / 78 (1.28%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			

subjects affected / exposed	1 / 78 (1.28%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 78 (0.00%)	3 / 74 (4.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	2 / 78 (2.56%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Brain injury			
subjects affected / exposed	0 / 78 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Convulsion			
subjects affected / exposed	0 / 78 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cerebral infarction			
subjects affected / exposed	0 / 78 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Ischaemic stroke			
subjects affected / exposed	1 / 78 (1.28%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 78 (1.28%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			

subjects affected / exposed	1 / 78 (1.28%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 78 (1.28%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 78 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 78 (1.28%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Compartment syndrome			
subjects affected / exposed	0 / 78 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 78 (1.28%)	2 / 74 (2.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Bronchitis			
subjects affected / exposed	0 / 78 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal infection			
subjects affected / exposed	1 / 78 (1.28%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Incision site infection			
subjects affected / exposed	0 / 78 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 78 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	1 / 78 (1.28%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 78 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 78 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Malnutrition			
subjects affected / exposed	1 / 78 (1.28%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	FCH arm	Placebo arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	70 / 78 (89.74%)	61 / 74 (82.43%)	
Investigations			
C-reactive protein increased			
subjects affected / exposed	4 / 78 (5.13%)	3 / 74 (4.05%)	
occurrences (all)	4	3	

White blood cell count increased			
subjects affected / exposed	0 / 78 (0.00%)	4 / 74 (5.41%)	
occurrences (all)	0	4	
Injury, poisoning and procedural complications			
Wound complication			
subjects affected / exposed	9 / 78 (11.54%)	8 / 74 (10.81%)	
occurrences (all)	9	8	
Procedural pain			
subjects affected / exposed	8 / 78 (10.26%)	5 / 74 (6.76%)	
occurrences (all)	8	5	
Post procedural haemorrhage			
subjects affected / exposed	4 / 78 (5.13%)	2 / 74 (2.70%)	
occurrences (all)	4	2	
Procedural haemorrhage			
subjects affected / exposed	5 / 78 (6.41%)	1 / 74 (1.35%)	
occurrences (all)	5	1	
Vascular disorders			
Hypotension			
subjects affected / exposed	10 / 78 (12.82%)	11 / 74 (14.86%)	
occurrences (all)	10	11	
Hypertension			
subjects affected / exposed	2 / 78 (2.56%)	6 / 74 (8.11%)	
occurrences (all)	2	6	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	33 / 78 (42.31%)	30 / 74 (40.54%)	
occurrences (all)	35	31	
Pericardial effusion			
subjects affected / exposed	4 / 78 (5.13%)	6 / 74 (8.11%)	
occurrences (all)	4	6	
Tachycardia			
subjects affected / exposed	1 / 78 (1.28%)	4 / 74 (5.41%)	
occurrences (all)	1	4	
Ventricular tachycardia			
subjects affected / exposed	4 / 78 (5.13%)	0 / 74 (0.00%)	
occurrences (all)	4	0	

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	15 / 78 (19.23%)	18 / 74 (24.32%)	
occurrences (all)	15	19	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	9 / 78 (11.54%)	5 / 74 (6.76%)	
occurrences (all)	9	5	
Oedema peripheral			
subjects affected / exposed	5 / 78 (6.41%)	3 / 74 (4.05%)	
occurrences (all)	5	3	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	9 / 78 (11.54%)	2 / 74 (2.70%)	
occurrences (all)	9	2	
Diarrhoea			
subjects affected / exposed	5 / 78 (6.41%)	3 / 74 (4.05%)	
occurrences (all)	5	3	
Constipation			
subjects affected / exposed	2 / 78 (2.56%)	5 / 74 (6.76%)	
occurrences (all)	2	5	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	18 / 78 (23.08%)	16 / 74 (21.62%)	
occurrences (all)	18	17	
Pneumothorax			
subjects affected / exposed	3 / 78 (3.85%)	4 / 74 (5.41%)	
occurrences (all)	3	4	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	10 / 78 (12.82%)	11 / 74 (14.86%)	
occurrences (all)	10	11	
Delirium			
subjects affected / exposed	6 / 78 (7.69%)	4 / 74 (5.41%)	
occurrences (all)	6	4	
Renal and urinary disorders			

Oliguria			
subjects affected / exposed	4 / 78 (5.13%)	5 / 74 (6.76%)	
occurrences (all)	4	5	
Renal failure acute			
subjects affected / exposed	2 / 78 (2.56%)	5 / 74 (6.76%)	
occurrences (all)	2	5	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	4 / 78 (5.13%)	2 / 74 (2.70%)	
occurrences (all)	4	2	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	7 / 78 (8.97%)	8 / 74 (10.81%)	
occurrences (all)	7	8	
Hypokalaemia			
subjects affected / exposed	4 / 78 (5.13%)	5 / 74 (6.76%)	
occurrences (all)	4	6	
Hypovolaemia			
subjects affected / exposed	3 / 78 (3.85%)	5 / 74 (6.76%)	
occurrences (all)	3	5	
Dehydration			
subjects affected / exposed	4 / 78 (5.13%)	2 / 74 (2.70%)	
occurrences (all)	4	3	
Hypocalcaemia			
subjects affected / exposed	4 / 78 (5.13%)	2 / 74 (2.70%)	
occurrences (all)	4	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 February 2013	The primary purpose of Amendment 1 of the clinical protocol was to allow the enrolment of subjects undergoing reoperation (resternotomy or rethoracotomy). The following main changes were made in this amendment: • Modification of an exclusion criterion to allow the inclusion of subjects undergoing reoperative aortic procedures (ie, resternotomy and rethoracotomy). Subjects undergoing reoperative aortic surgery at the same anatomic site as the original procedure, such as replacement of a previously placed aortic graft, were to continue to be excluded. • Reduction in the number of assessments requiring blood samples from study subjects. • Inclusion of additional biochemistry assessments. • Addition of health care resource utilization exploratory endpoints. • Clarification of the definition of unblinding, particularly in reference to access by study personnel to the results of fibrinogen assessments. • To clarify statements regarding: clinical procedures and assessments, concomitant medications and analysis populations.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Markers of coagulopathic bleeding (eg, plasma fibrinogen level, platelet count) are likely to be more appropriate indicators of the need for allogeneic blood product transfusion than the 5-minute bleeding mass assessment used in this study.

Notes: