FIBCON trial

End of Trial Report for EudraCT

Date:	November 30th, 2018
Report Author:	Dr Shane Tibby
Study Title:	Fibrinogen concentrate supplementation in the management of bleeding during paediatric cardiopulmonary bypass: a phase1B/2A, open label dose escalation study (FIBCON)
Sponsor:	Guy's & St Thomas' NHS Foundation Trust
Funder:	CSL Behring UK Ltd
Chief Investigator:	Dr Shane Tibby
Study numbers:	EudraCT: 2013-003532-68 ISRCTN: 50553029 REC: 14/LO/0267 UKCRN ID: 16254: FIBCON

1. Summary

This report details the findings of the trial entitled “Fibrinogen concentrate supplementation in the management of bleeding during paediatric cardiopulmonary bypass: a phase 1B/2A, open label dose escalation study (FIBCON)”. The report has been prepared for uploading to EudraCT.

2. Introduction

The FIBCON trial is a first step in testing the overarching hypothesis: Fibrinogen concentrate supplementation during paediatric cardiopulmonary bypass may decrease the incidence and severity of postoperative bleeding, and reduce the need for transfusion of blood and ancillary blood products (platelets, fresh frozen plasma, and cryoprecipitate).

The trial was of an early phase design, examining specifically:

Primary Objective:
To determine the dose of intraoperative fibrinogen concentrate required to achieve physiological levels of fibrin polymerization of 8 to 13 mm as measured by the rotational thromboelastometry (ROTEM) measure of fibrin-based clotting: FibTEM MCF (equating to plasma fibrinogen concentrations of 1.5 to 2.5 g/L), immediately prior to separation from cardiopulmonary bypass in neonates and infants < 12kg.

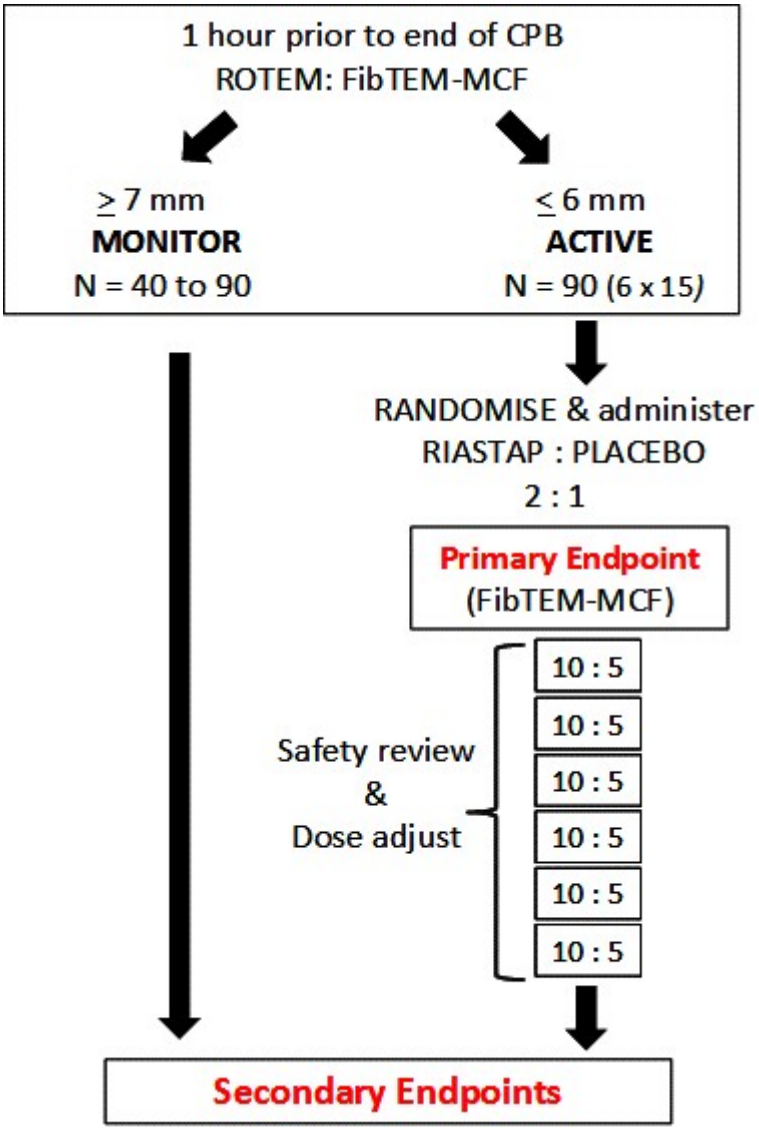
Secondary Objectives:
(a) To provide preliminary efficacy and safety data
(b) To document ROTEM profiles intra- and post-operatively

Although classed as open label; the administration of IMP/placebo was known only to the study team administering the study drug. Clinical staff, patients and those collecting and adjudicating the safety and efficacy data were blinded.

Full study details are contained in the protocol (version 1.0, January 28, 2014)

Several aspects of the trial design are novel in this patient population: (i) targetting high risk patients intraoperatively using a point of care test for coagulation (rotational thromboelastometry, ROTEM), (ii) IMP dosing while the patient is undergoing cardiopulmonary bypass, (iii) individualised dosing using ROTEM values and a bedside drug calculator.

3. Study Flow Diagram

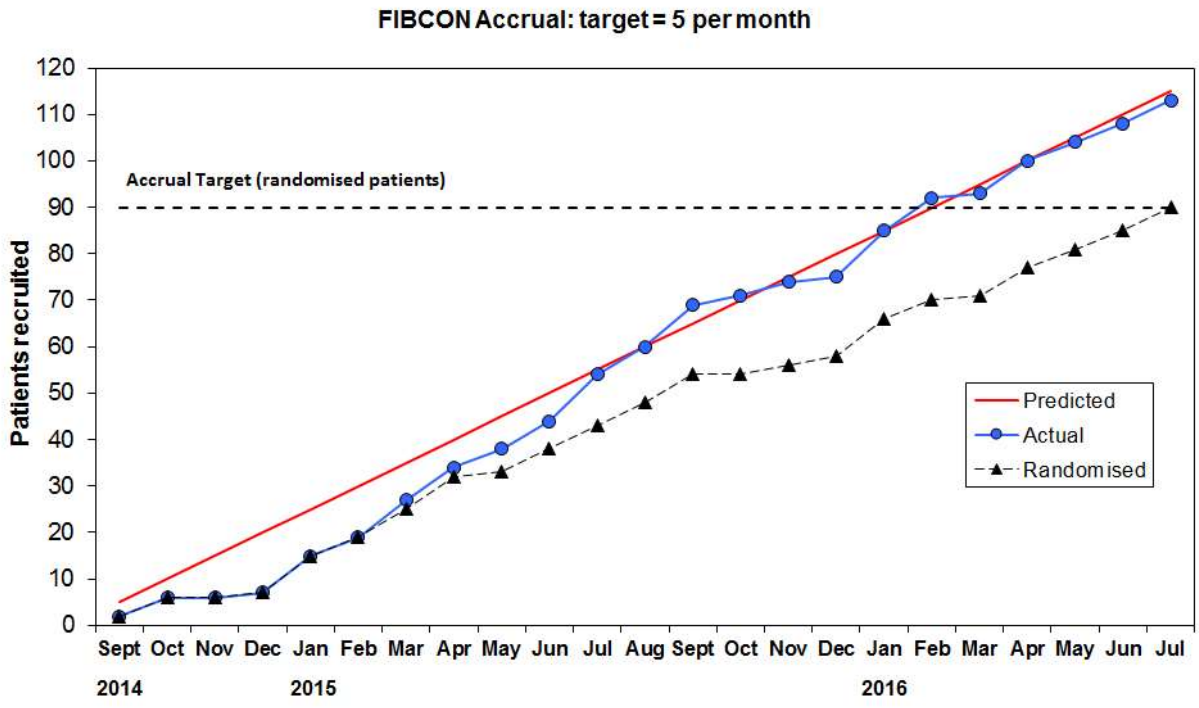


Of note, the dosing algorithm proved accurate in terms of achieving fibrinogen plasma levels within the required therapeutic range; thus dose adjustment / escalation was not required

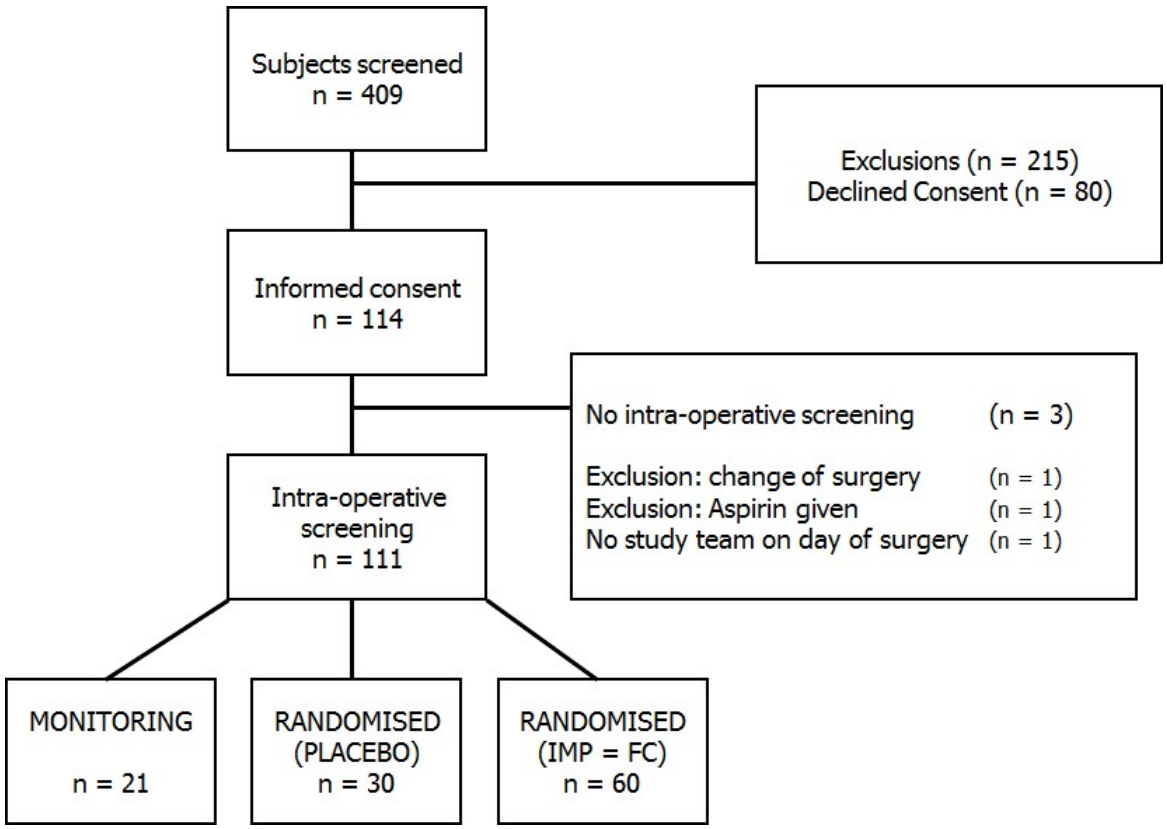
4. Trial Milestones and Accrual

REC approval: 11 / 03 / 2014
MHRA approval: 11 / 03 / 2014
R&D approval: 29 / 07 / 2014 (trial team not informed until 11 / 08 / 2014)
Trial Open: 01 / 09 / 2014
First Recruit: 22 / 09 / 2014
Last Recruit: 20 / 07 / 2016
Trial Closure: 21 / 08 / 2016

Accrual graph



Screening / Consent



Exclusions (n = 215)

	Reason	n
1	Shunt dependent circulation	25
2	Transposition of Great Arteries	20
3	No bypass surgery	47
4	Significant co-morbidity	10
5	Inherited coagulopathy/thrombophilia	1
6	Aspirin taken < 48hrs pre-op	4
7	<36 weeks corrected gestation	0
8	Major thrombosis in previous 2 weeks	1
9	Renal / Liver impairment < 2 days pre-op	1
10	Known allergy to drug / related product	0
11	History of anaphylaxis	0
12	Enrolled in another interventional trial < 3 mths	0
13	Other	87
14	PI decision not to recruit	19
		215

Research staff availability (consent)	16
Research staff availability (day of surgery)	20
High risk	3
Likely short bypass	9
Surgery too short notice	20
Language barrier	8
Parent non available	4
Chain of Hope patient	2
Parents missed on pre-admission	4
ineffective screen (no coag results avail)	1
	87

Difficult intra-op / post-op time	8
Likely short bypass	2
Likely duct dependent post op (stent)	1
High risk	8
	19

Patient Demographics

	MONITORING	ACTIVE		Total
	(n = 21)	FC (n = 60)	Placebo (n = 30)	(n = 111)
Age (months, mean (SD))	7 (5.7)	6 (5.1)	6.9 (7.2)	6.4 (5.8)
Weight (kg, mean (SD))	6 (1.7)	5.9 (2.1)	5.8 (2.2)	5.9 (2.0)
Gender (% male)	38.1	50.0	56.7	49.6
CPB time (min, mean (SD))	98 (47)	104 (42)	102 (50)	102 (45)
Type of surgery (n)				
VSD closure	10	14	7	31
AVSD repair	5	11	5	21
TOF repair	2	11	5	18
Hemifontan/Fontan	1	9	3	13
Arch repair	1	4	3	8
Truncus arteriosus repair	1	2	2	5
Pulmonary atresia repair	0	2	2	4
Combined Norwood 1&2	1	1	1	3
Norwood 1	0	2	0	2
Arterial Switch Operation	0	2	0	2
RVOTO/LVOTO relief	0	1	1	2
VSD and ASD closure	0	0	1	1
TAPVD repair	0	1	0	1

5. Protocol Deviations & Monitoring

Deviation	Study Number	Explanation
Study drug still infusing as patient came off of bypass & protamine given	01/001	Sample T2a and T3 run as one sample
Blood samples FBC T2, T2a & T5 (GSTT) missing	01/001	Lab cancelled sample
T2 Coag sample (GSTT) not done	01/001	Lab cancelled sample
Patient unblinded	01/001	Concerns re abnormal clotting, ?study drug side effect– pt received placebo
T5 sample not done	01/002, 01/007	Lab cancelled sample
T5 Coagulation sample clotted	05/013	Sample clotted
T5 Coagulation sample delayed	04/002	Patient in catheter laboratory, sample taken on return from cath lab
Haematology GSTT sample T1 missing	01/008	Sample diluted
Coagulation GSTT sample missing T2	01/008, 089	Sample diluted / lab error
T2a sample missing	01/010	Lab cancelled sample
T2a Sample missing	01/057	Sample spun by mistake
T6 Haematology sample missing	01/012	Sample clotted
T4 Haematology sample GSTT missing	01/015, 02/002	Sample clotted
T4 Clotting profile missing	02/002, 06/003	Sample clotted / cancelled by laboratory
T3 platelet result missing	02/006	Clumped sample
T6 sample taken early	02/007, 02/010, 05/005, 089, 06/013	Line to be removed
T0 samples missing	02/011	Not received in lab
Sample T1 and T2 taken at the same time-point (i.e. merged into a single sample)	02/012, 03/003, 03/004, 03/006, 03/008, 03/011, 03/012, 03/015, 04/001, 04/003, 04/004, 061, 04/005, 04/007, 071, 05/005, 090, 05/012, 06/002, 06/003, 06/010, 06/011	Due to short bypass time i.e. less than 1 hour
Desired MCF changed to 9	01/002 – 06/015	CI Decision
Drug not given	01/005	Surgeon's decision to come off bypass before drug preparation completed
Study drug not completed before coming off bypass and post protamine	01/013	Cause uncertain, as this does not equate with timelines documented in CRF, where timings suggest drug given fully. Awaiting further review of case notes and perfusion records

Deviation	Study Number	Explanation
Study drug given into CPB circuit	04/002	Surgeon request as concerned re CVL site
Patient eligible but not randomised (MCF 6)	048	CI decision not to randomise due to significant ST depression following anaesthetic induction
No ALT result available on re-screening date (original surgery deferred)	077	Original ALT results within expected limits, clinical decision taken by Research Fellow to include patient. ALT post-operatively within expected limits
Patient not included in study	053	Patient allocated study number but due to being taken for surgery over weekend not staff available to undertake study

Kings Health Partners CTO Monitoring visits FIBCON

08 Oct 2014	27 Nov 2014	26 Jan 2015	30 Mar 2015
29 May 2015	17 Jul 2015	21 Sept 2015	03 Nov 2015
18 Jan 2016	17 Mar 2016	02 Jun 2016	28 Jul 2016
29 Sep 2016	14 Dec 2016	25 Jan 2017	

- No significant issues raised.

6. Thrombosis Summary and Graphs

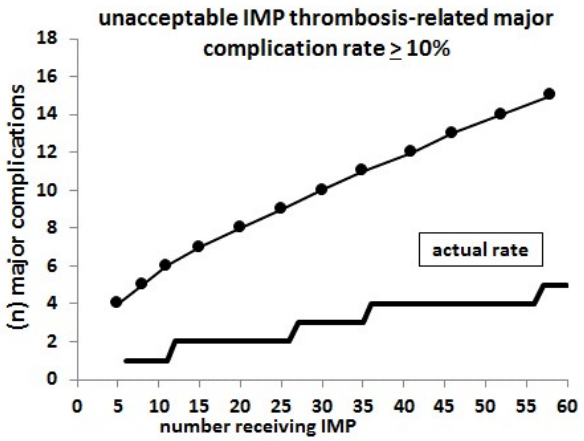
The thromosis and thrombus-related major complication rates were well below the unacceptable limits as defined in the protocol.

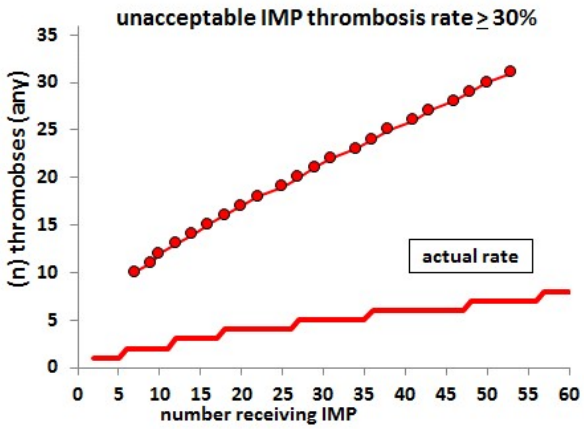
Summary data are shown below for the entire population.

12 x thromboses occurred in 10 patients (8 IMP 2 placebo), of which:

5 x	represented potential thrombosis-related major complications	
	- ? suspected Left pulmonary artery thrombus	IMP
	- occlusion of BT shunt D6 post study drug	IMP
	- septic emboli in toes	IMP
	- splenic infarction	IMP
	- suspected intracardiac thrombus	IMP
7 x	were line-related	5 IMP / 2 placebo

One patient (IMP) had 3 thromoses: 1 splenic infarction and 2 line-related





NB: graphs above refer to unacceptable rates in the IMP arm only. Plots refer to individual patients receiving IMP. Patients with multiple thrombi are plotted once only, ascribed according to the major thrombus incurred.

Expert members on the Trial Steering Committee have reviewed blinded, detailed data for individual cases, including case summaries, relevant imaging, operative notes, etc. In all cases, a potential alternative reason for thrombus has been identified (e.g. anatomical narowing of a vessel).

Study ID	Rand. No.	Group	wgt	Surgery	Randomised	Date study complete	Date Thrombus	Thromb. No.	Thrombosis diagnosis	Thrombosis risk factors	Other
001A	01001	plac	2.8	truncus arteriosus	22/09/2014	04/10/2014	24/09/2014	1	Right SFA/CFA arterial thrombus. Right CFV and EIV venous thrombus (occlusive)	right femoral venous and arterial lines	6 weeks LMWH. Haematology Review: Thrombosis resolved, no further investigation required
004A	01004	IMP	6.9	DKS & Hemifontan	10/10/2014	17/10/2014	13/10/2014	1	suspicion for thrombus left external iliac vein	left femoral venous and arterial lines	6 weeks LMWH. Haematology Review: Thrombosis resolved, no further investigation required
010A	01010	IMP	5.8	NW 1&2 combined	08/01/2015	27/01/2015	08/10/2015	1	hypoxia intraop, cath lab: SVC filling defect at LPA takeoff with normal distal branch calibre	small LPA noted preop on MRI and intraop noted by surgeon	LPA stented post op. aspirin only at discharge
017A	02002	IMP	5.1	VSD	19/02/2015	03/03/2015	26/02/2015	1	flail echo on VSD patch noted on routine postop echo	recurrent infections preop; arrhythmia postop requiring pacing; central venous line in situ RIJ	Not definite thrombus. Given iv heparin, but no further anticoagulation at D/C
019A	02004	plac	3.9	AVSD	24/02/2015	07/03/2015	01/03/2015	1	short segment, non-occlusive right distal EIA thrombus	right femoral arterial line	clot non occlusive, resolved with line removal, no Rx

Study ID	Rand. No.	Group	wgt	Surgery	Randomised	Date study complete	Date Thrombus	Thromb. No.	Thrombosis diagnosis	Thrombosis risk factors	Other
029A	02012	IMP	5.9	Hemifontan	17/04/2015	26/04/2015	21/04/2015	1	cool right leg with absent pulses, no occlusive thrombus on imaging, non-occlusive thrombus could not be excluded	right femoral arterial and venous lines	6 weeks LMWH. Haematology Review: Thrombosis resolved, no further investigation required
050A	03010	IMP	3.5	AVSD hypoplastic arch	22/07/2015	02/08/2015	27/07/2015	1	limb swelling and dusky colour of right leg, no thrombosis on imaging	right femoral venous line; previous long line in right leg; severe LCOS with organ dysfunction & coagulopathy; multiple blood products, sepsis	care withdrawn in light of refractory LCOS with worsening end organ dysfunction
050A	03010	IMP	3.5	AVSD hypoplastic arch	22/07/2015	02/08/2015	28/07/2015	2	an extensive left external iliac vein thrombus extending to the left common femoral vein	left femoral 3-lumen venous line; severe LCOS with organ dysfunction & coagulopathy; multiple blood product, sepsis	care withdrawn in light of refractory LCOS with worsening end organ dysfunction
050A	03010	IMP	3.5	AVSD hypoplastic arch	22/07/2015	02/08/2015	30/07/2015	3	Splenic infarction	severe LCOS with organ dysfunction incl coagulopathy; multiple blood product infusions, sepsis	care withdrawn in light of refractory LCOS with worsening end organ dysfunction

Study ID	Rand. No.	Group	wgt	Surgery	Randomised	Date study complete	Date Thrombus	Thromb. No.	Thrombosis diagnosis	Thrombosis risk factors	Other
069A	4009	IMP	6.4	pulm atresia VSD	24/09/2015	16/10/2015	15/10/2015	1	dusky toes bilaterally / microemboli	severe LCOS with end organ dysfunction, fungal sepsis	care withdrawn in light of refractory LCOS with worsening end organ dysfunction
095A	05013	IMP	3.6	AVSD	06/04/2016	21/04/2016	09/04/2016	1	right femoral arterial and venous thrombus	LCOS, arrhythmia, arterial and venous catheter in same leg	Observation only. Leg improved after removal of line
109A	06011	IMP	3.5	Norwood 1	01/07/2016	29/07/2016	06/07/2016	1	Blocked BT shunt	BT-Shunt, heparin paused as overshooting antiXa on 03/07 and clinical bleeding, after restarting difficulty to achieve therapeutic antiXa (0.03 on 06/07)	surgical exploration and un-wrapping of shunt. No thrombus visualised (opaque tube), immediate improvement after milking and unwrapping of shunt

7. AE / SAE / SUSAR

No SAEs, SARs or SUSARs reported, as at February 14th, 2017

Table of AEs

Study ID	Rand. No.	Date randomised	Group	Date study completed	Thrombus	SAE	AE no.	AE dx	AE date	AE resolution	AE relation to IMP	AE expected	AE severity	AE action taken	AE outcome
001	01001	22/09/14	plac	04/10/2014	Y	N	1	sinus tachycardia	22/09/14	22/09/2014	possibly	expected	mild	none	resolved
019	02004	24/02/15	plac	07/03/2015	Y	N	1	tear of stomach on PD cath insertion	24/02/15	NA	unlikely	unexpected	mild	tear sutured	resolved
035	03003	08/05/15	IMP	13/11/2015	N	N	1	tachycardiac and hypotension	08/05/15	08/05/2015	possibly	expected	mild	concomitant medication	resolved
035	03003	08/05/15	IMP	13/11/2015	N	N	2	ST elevation	09/05/15	09/05/2015	possibly	unexpected	mild	concomitant medication	resolved
044	03008	29/06/15	plac	09/07/2015	N	N	1	ST depression, tachycardia, hypotension, chest re-opened	29/06/15	01/07/2015	unlikely	unexpected	mod	surgical exploration	resolved
044	03008	29/06/15	plac	09/07/2015	N	N	2	abrasion to stomach on PD cath insertion	29/07/15	NA	unlikely	unexpected	mild	none	resolved
048	NA	NA	cohort	19/07/2015	N	N	1	persistent ST-elevation in OT before CPB	14/07/15	14/07/2015	unlikely	unexpected	mod	surgical exploration	resolved

Study ID	Rand. No.	Date randomised	Group	Date study completed	Thrombus	SAE	AE no.	AE dx	AE date	AE resolution	AE relation to IMP	AE expected	AE severity	AE action taken	AE outcome
050	03010	22/07/15	IMP	02/08/2015	Y	N	1	unusually severe' hypotension with lactic acidosis post bypass	22/07/15	26/07/2015	possibly	unexpected	mod	concomitant medication	resolved
050	03010	22/07/15	IMP	02/08/2015	Y	N	2	chest re-exploration to relieve pericardial effusion	23/07/15	23/07/2015	unlikely	unexpected	mod	surgical exploration	resolved
050	03010	22/07/15	IMP	02/08/2015	Y	N	3	chest re-explored relieve pleural effusion	28/07/15	28/07/2015	unlikely	unexpected	mod	surgical exploration	resolved
064	04006	10/09/15	plac	07/10/2015	N	N	1	insufficient heparinisation, low AT3, AT3 conc. given	10/09/15	10/09/2015	unlikely	unexpected	mild	concomitant medication	resolved
064	04006	10/09/15	plac	07/10/2015	N	N	2	pulm. haemorrh & difficult ventil on PICU adm.	10/09/15	10/09/2015	unlikely	unexpected	mod	concomitant medication / ventilation	resolved
069	04009	24/09/15	IMP	16/10/2015	Y	N	1	pulmonary haemorrhage	26/09/15	26/09/2015	unlikely	unexpected	mod	concomitant medication / ventilation	resolved
069	04009	24/09/15	IMP	16/10/2015	Y	N	2	chest re-explored as in LCOS	26/09/15	NA	unlikely	unexpected	mod	surgical exploration	resolved
069	04009	24/09/15	IMP	16/10/2015	Y	N	3	tension pneumothorax	05/10/15	05/10/2015	unlikely	unexpected	mod	surgical exploration/ chest drain	resolved
069	04009	24/09/15	IMP	16/10/2015	Y	N	4	cerebral occipital haematoma / empyema	08/10/15	NA	unlikely	unexpected	mod	none	unknown
069	04009	24/09/15	IMP	16/10/2015	Y	N	5	inominate vein punctured during CVC insertion, chest re-opened	09/10/15	09/10/2015	unlikely	unexpected	mod	surgical exploration	resolved

Study ID	Rand. No.	Date randomised	Group	Date study completed	Thrombus	SAE	AE no.	AE dx	AE date	AE resolution	AE relation to IMP	AE expected	AE severity	AE action taken	AE outcome
069	04009	24/09/15	IMP	16/10/2015	Y	N	6	chest re-explored pleural effusion and toilet in view of sepsis	02/10/15	02/10/2015	unlikely	expected	mild	surgical exploration	resolved
072	04010	05/11/15	IMP	05/11/2015	N	N	1	flushing noted after surgical drapes removed	05/11/15	05/11/2015	possible	unexpected	mild	none	resolved
088	NA	05/02/16	plac	01/03/2016	N	N	1	brief run of self-limiting VT (<60 sec)	05/02/16	05/02/2016	unlikely	unexpected	mild	none	resolved
087	05008	11/02/16	IMP	21/02/2016	N	N	1	SVT on dissection during chest opening (volume loaded enlarged heart)	11/02/16	11/02/2016	unlikely	unexpected	moderate	shocked to cardiovert	resolved
087	05008	11/02/16	IMP	21/02/2016	N	N	2	hypoxia after coming off bypass	11/02/2016	11/02/2016	unlikely	unexpected	mild	ventilation	resolved
096	05014	12/04/16	IMP	12/05/2016	N	N	1	bowel perforation on insertion of PD cath, oversewn	12/04/16	NA	unlikely	unexpected	mild	surgical exploration/ oversewn	unknown
100	06002	26/04/16	plac	26/05/2016	N	N	1	cardiorespiratory arrest	29/04/16	29/04/2016	unlikely	unexpected	moderate	admission to PICU	resolved
101	06003	05/05/16	IMP	11/05/2016	N	N	1	SVT on dissection during chest opening	05/05/16	05/05/2016	unlikely	unexpected	moderate	shocked to cardiovert	resolved
103	06005	19/05/16	IMP	12/06/2016	N	N	1	ST depression pre bypass	19/05/16	19/05/2016	unlikely	unexpected	mild	none	resolved

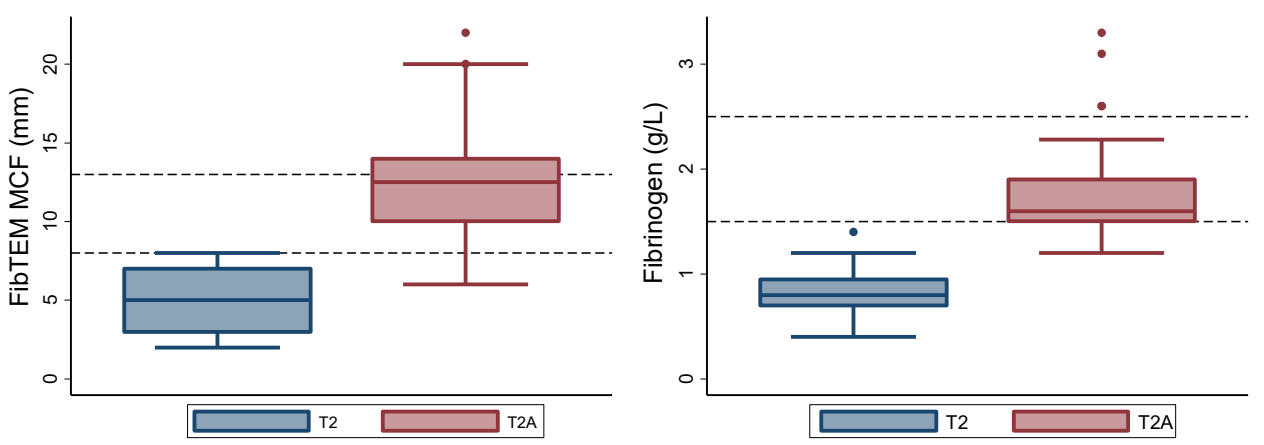
Study ID	Rand. No.	Date randomised	Group	Date study completed	Thrombus	SAE	AE no.	AE dx	AE date	AE resolution	AE relation to IMP	AE expected	AE severity	AE action taken	AE outcome
103	06005	19/05/16	IMP	12/06/2016	N	N	2	hypoxia post CPB, bronchoscopy showing LMB compression and bleed/bruising from LMB	19/05/16	19/05/2016	unlikely	unexpected	moderate	ventilation, oxygen, bronchial lavage	resolved
104	06006	19/05/16	IMP	04/06/16	N	N	1	ST depression on postop ECG, on preop ECG was already present, VSD close to coronary origin	20/05/16	02/06/16	unlikely	unexpected	moderate	none	resolved
107	06008	14/06/16	plac	30/06/2016	N	N	1	abrasion to stomach PD cath insertion	14/06/16	14/06/2016	unlikely	unexpected	mild	none	resolved
107	06008	14/06/16	plac	30/06/2016	N	N	2	ST elevation & ++ hypotension off CPB, acutely appearing and resolving ?air in coronaries, good coron ECHO flow	14/06/16	14/06/2016	unlikely	unexpected	moderate	concomitant medication and CPB briefly restarted	resolved
108	06010	21/06/16	plac		N	N	1	hypoxia, hypotens & ischaemic ECG changes during prolonged period of dissection	21/06/16	21/06/2016	unlikely	unexpected	moderate	concomitant medication	resolved
109	06011	01/07/16	IMP		Y	N	1	SVT pre bypass during dissection	01/07/16	01/07/2016	unlikely	unexpected	moderate	shocked to cardiovert	resolved
109	06011	01/07/16	IMP		Y	N	2	mediastinal wash out as bleeding concerns, antiXa supratherapeutic	03/07/16	03/07/2016	unlikely	unexpected	moderate	mediastinal wash out, heparin paused	resolved
110	06012	07/07/16	IMP		N	N	1	ST changes after removal of cross clamp, visible air in coronaries	07/07/16	07/07/2016	unlikely	unexpected	mild	increase in BP to 'flush' coronaries	resolved

8. Primary endpoint: FibTEM MCF and Fibrinogen levels 5 minutes post dose (T2A)

The ROTEM-based dosing formula produced a consistent overshoot in FibTEM MCF (median achieved level 13mm, predicted level 9mm). However the precision was reasonable (interquartile range 10 to 14mm). A similar pattern was seen for achieved fibrinogen levels. Fibrinogen levels post-dosing were within the targeted range of 1.5 to 2.5 g/L in 43/60 (72%) patients receiving IMP. Of not, all patients achieved a fibrinogen level >1.0 g/L (minimum 1.2 g/L), and none would be deemed supratherapeutic (maximum 3.3 g/L).

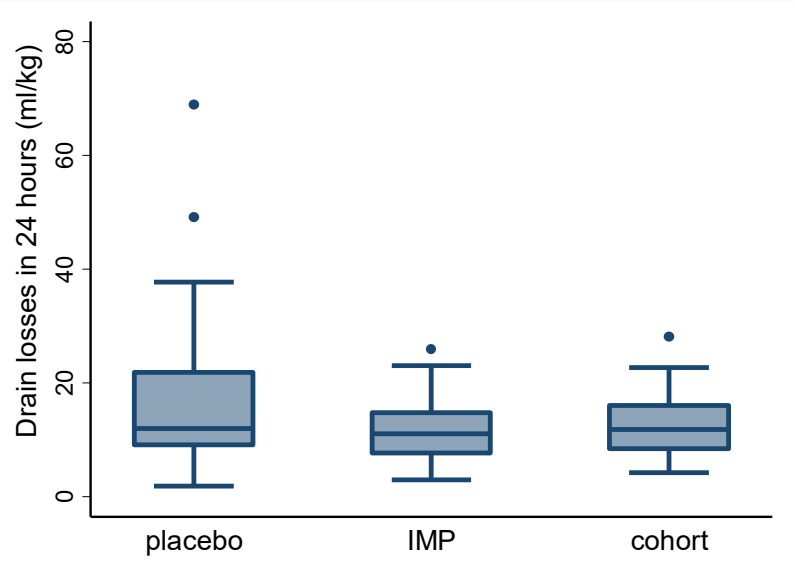
This was achieved using an adminsitered TOTAL fibrinogen concentrate dose of 51 to 218 mg/kg. However, this dose includes a factor to incorporate the extracorporeal circuit; the equivalent dose range for patients not receiving cardiopulmonary bypass would be 31 to 87 mg/kg (table).

stats	Fibrinogen(g/L)		FibTEM MCF(mm)		Fibrinogen dose(mg/kg)	
	T2	T2A	T2	T2A	TOTAL	PATIENT
max	1.4	3.3	8	22	218	87
p90	1.1	2.2	8	18	184	74
p75	1.0	1.9	7	14	138	69
p50	0.8	1.6	5	13	114	54
p25	0.7	1.5	3	10	81	41
p10	0.6	1.4	3	9	63	32
min	0.4	1.2	2	6	51	31
N	60	60	60	60	60	60



Fibrinogen (left) and FibTEM MCF (right) levels achieved pre- and post dosing (time point T2 and T2A). Dashed lines represent desired range at T2A, according to the protocol.

9. Secondary endpoint: efficacy (24 hour mediastinal drain loss & blood product use)



Drain drain loss in 24 hrs (ml/kg)	Mean	SD
placebo	17.1	14.3
IMP	11.6	5.2
cohort	12.6	6.4
Total	13.3	9.0

Analysis of Variance

Source	SS	df	MS	F	Prob > F
Between groups	606.62	2	303.31	3.91	**0.023**
Within groups	8367.44	108	77.48		
Total	8974.05	110	81.58		

Post hoc comparisons: Bonferroni-corrected P value

IMP vs placebo	**0.02**
IMP vs cohort	1.0
Placebo vs cohort	0.23

Post operative blood product use

blood_any	IMP or placebo: placebo	IMP	cohort	Total
none	12	35	14	61
	40.00	58.33	66.67	54.95
blood product	18	25	7	50
	60.00	41.67	33.33	45.05
Total	30	60	21	111
	100.00	100.00	100.00	100.00

Fisher's exact = 0.126

```
. nptrend blood_any, by(gp)
            gp        score          obs   sum of ranks
       placebo            0           30           1929
           IMP            1           60         3247.5
        cohort            2           21         1039.5

          z  = -1.96
  Prob > |z| = 0.050
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