Clinical trial results:
Fibrinogen concentrate supplementation in the management of bleeding during paediatric cardiopulmonary bypass: a phase 1B/2A, open label dose escalation study (Version 1.0, Jan 28, 2014)

Summary

EudraCT number	2013-003532-68
Trial protocol	GB
Global end of trial date	29 July 2016

Results information

Result version number	v1 (current)
This version publication date	20 December 2018
First version publication date	20 December 2018
Summary attachment (see zip file)	FINAL STUDY REPORT (FIBCON End of Trial Report for EudraCT Nov 30 2018.pdf)

Trial information

Trial identification

Sponsor protocol code	FIBCON

Additional study identifiers

ISRCTN number	ISRCTN50553029
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Guy's and St Thomas' NHS Foundation Trust
Sponsor organisation address	Great Maze Pond, London, United Kingdom, SE19RT
Public contact	Dr Shane Tibby, Guy's and St Thomas' NHS Foundation Trust, 44 0207188 4572 , shane.tibby@gstt.nhs.uk
Scientific contact	Dr Shane Tibby, Guy's and St Thomas' NHS Foundation Trust, 44 0207188 4572 , shane.tibby@gstt.nhs.uk

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	29 July 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 July 2016
Global end of trial reached?	Yes
Global end of trial date	29 July 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the dose of intraoperative human fibrinogen concentrate required to achieve physiological levels of fibrin polymerization of 8 to 13 mm as measured by the 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 children < 12kg

Protection of trial subjects:

For patients in the active arm, the drug will be administered in a non-blinded fashion, according to manufacturer's instructions, via a dedicated lumen of the central venous line, while the patient is still on cardiopulmonary bypass, at time T2 (approximately 1
hour prior to separation from CPB).
Administration of study drug while still on CPB represents a major departure from adult trials; however this design was chosen to maximise safety, due to the potential for (a)drug hypersensitivity/allergic reactions and (b) acute vascular occlusion in this patient
group (a life threatening complication)

Background therapy:

Not applicable

Evidence for comparator: -

Actual start date of recruitment	19 September 2014
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	United Kingdom: 111
Worldwide total number of subjects	111
EEA total number of subjects	111

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)	111

Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from one clinical site in London during 2014 to 2016.

Pre-assignment

Screening details:

Inclusion Criteria
i) Congenital heart disease requiring non-emergency* surgery on cardiopulmonary bypass
ii) Age range: > 36 weeks corrected gestation
iii) Weight 2.5 – 12 kg
iv) Informed consent to participate
*Non-emergency is defined as surgery that can be delayed .24 hours following diagnosis of congenital heart disease

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind[1]
Roles blinded	Subject, Carer, Assessor

Blinding implementation details:

Randomised, placebo controlled, , dose escalation study. Trial team not blinded.
Treating clinicians and patients will blinded to allocation to reduce bias with respect to the secondary objectives of (a) safety (adverse event reporting) and (b) efficacy (ancillary blood products administered).

Arms

Are arms mutually exclusive?	Yes
Arm title	MONITOR GROUP

Arm description:

In instances of screening failure (FibTEM MCF >7mm), patients will not be randomised, and will undergo data collection only (as per study protocol) - MONITOR arm
1 hour prior to end of CPB - ROTEM: FibTEMMCF,
If > 7 mm < 6 mm - recruited to MONITOR arm

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	ACTIVE GROUP

Arm description:

For patients in the active arm, the drug will be administered in a non-blinded fashion, according to manufacturer's instructions, via a dedicated lumen of the central venous line, while the patient is still on cardiopulmonary bypass, at time T2 (approximately 1 hour prior to separation from CPB). The administering clinician will monitor closely for signs of flushing, rash, hypotension or requirement for increased CPB circuit fluid supplementation. Upon recommencement of mechanical ventilation, the clinician will monitor for signs of wheeze, unexplained hypoxia or hypercarbia, and decreased chest compliance as shown by need for increased ventilatory pressures.

Arm type	Experimental
Investigational medicinal product name	RIASTAP
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

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.

Arm title	PLACEBO GROUP
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	sodium chloride 0.9% solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients will be administered placebo only if they meet screening criteria at T2 (one hour prior to separation from CPB), as evidenced by: FibTEM MCF <6mm.

Notes:

[1] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.
Justification: Treating clinicians and patients were blinded to allocation, Trial team were not blinded.

Number of subjects in period 1	MONITOR GROUP	ACTIVE GROUP	PLACEBO GROUP
Started	21	60	30
Completed	21	60	30

Baseline characteristics

Reporting groups

Reporting group title	MONITOR GROUP

Reporting group description:

In instances of screening failure (FibTEM MCF >7mm), patients will not be randomised, and will undergo data collection only (as per study protocol) - MONITOR arm
1 hour prior to end of CPB - ROTEM: FibTEMMCF,
If > 7 mm < 6 mm - recruited to MONITOR arm

Reporting group title	ACTIVE GROUP

Reporting group description:

For patients in the active arm, the drug will be administered in a non-blinded fashion, according to manufacturer's instructions, via a dedicated lumen of the central venous line, while the patient is still on cardiopulmonary bypass, at time T2 (approximately 1
hour prior to separation from CPB). The administering clinician will monitor closely for signs of flushing, rash, hypotension or requirement for increased CPB circuit fluid supplementation. Upon recommencement of mechanical ventilation, the clinician will monitor for signs of wheeze, unexplained hypoxia or hypercarbia, and decreased chest compliance as shown by need for increased ventilatory pressures.

Reporting group title	PLACEBO GROUP

Reporting group description: -

Reporting group values	MONITOR GROUP	ACTIVE GROUP	PLACEBO GROUP
Number of subjects	21	60	30
Age categorical Units: Subjects			
Preterm newborn infants (gestational age < 37 wks)	21	60	30
Gender categorical Units: Subjects			
Female	13	30	13
Male	8	30	17

Reporting group values	Total		
Number of subjects	111		
Age categorical Units: Subjects			
Preterm newborn infants (gestational age < 37 wks)	111		
Gender categorical Units: Subjects			
Female	56		
Male	55		

End points

End points reporting groups

Reporting group title	MONITOR GROUP

Reporting group description:

In instances of screening failure (FibTEM MCF >7mm), patients will not be randomised, and will undergo data collection only (as per study protocol) - MONITOR arm
1 hour prior to end of CPB - ROTEM: FibTEMMCF,
If > 7 mm < 6 mm - recruited to MONITOR arm

Reporting group title	ACTIVE GROUP

Reporting group description:

For patients in the active arm, the drug will be administered in a non-blinded fashion, according to manufacturer's instructions, via a dedicated lumen of the central venous line, while the patient is still on cardiopulmonary bypass, at time T2 (approximately 1
hour prior to separation from CPB). The administering clinician will monitor closely for signs of flushing, rash, hypotension or requirement for increased CPB circuit fluid supplementation. Upon recommencement of mechanical ventilation, the clinician will monitor for signs of wheeze, unexplained hypoxia or hypercarbia, and decreased chest compliance as shown by need for increased ventilatory pressures.

Reporting group title	PLACEBO GROUP

Reporting group description: -

Primary: Primary Objective

End point title	Primary Objective[1][2]

End point description:

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 fibrinbased 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.

End point type	Primary

End point timeframe:

During cardiac surgery immediately prior to cardiopulmonary bypass separation.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Please see attached document for all values and results.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The MONITOR group was not, nor intended to be analysed for Primary Objective or Endpoint.

End point values	ACTIVE GROUP	PLACEBO GROUP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	30		
Units: decimal	60	30		

Attachments (see zip file)	PRIMARY ENDPOINT/Primary Endpoint.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Objective

End point title	Secondary Objective

End point description:

Secondary Objectives:
(a) To provide preliminary efficacy and safety data
(b) To document ROTEM profiles intra and postoperatively
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.

End point type	Secondary

End point timeframe:

During cardiac surgery immediately prior to cardiopulmonary bypass separation.

End point values	MONITOR GROUP	ACTIVE GROUP	PLACEBO GROUP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	60	30	
Units: decimal	21	60	30	

Attachments (see zip file)	SECONDARY ENDPOINT/Secondary Endpoint.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 0 to 30 days	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1
Reporting groups	
Reporting group title	ACTIVE GROUP
Reporting group description: -	
Reporting group title	PLACEBO GROUP
Reporting group description: -	
Reporting group title	MONITOR GROUP
Reporting group description: -	

Serious adverse events	ACTIVE GROUP	PLACEBO GROUP	MONITOR GROUP
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 60 (0.00%)	0 / 30 (0.00%)	0 / 21 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	ACTIVE GROUP	PLACEBO GROUP	MONITOR GROUP
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 60 (21.67%)	9 / 30 (30.00%)	1 / 21 (4.76%)
Congenital, familial and genetic disorders			
SVT on dissection during chest opening			
subjects affected / exposed	3 / 60 (5.00%)	0 / 30 (0.00%)	0 / 21 (0.00%)
occurrences (all)	3	0	0
Vascular disorders			
cerebral occipital haematoma / empyema			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			

sinus tachycardia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 30 (3.33%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
tachycardiac and hypotension			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
ST elevation			
subjects affected / exposed	1 / 60 (1.67%)	1 / 30 (3.33%)	1 / 21 (4.76%)
occurrences (all)	1	1	1
ST depression, tachycardia, hypotension			
subjects affected / exposed	0 / 60 (0.00%)	1 / 30 (3.33%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
unusually severe' hypotension with lactic acidosis post bypass			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Pericardial effusion			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Low Cardiac Output Syndrome			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
flushing			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
brief run of self- limiting VT (<60 sec)			
subjects affected / exposed	0 / 60 (0.00%)	1 / 30 (3.33%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
cardiorespiratory arrest			
subjects affected / exposed	0 / 60 (0.00%)	1 / 30 (3.33%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
ST depression pre bypass			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
ST depression postop ECG, on preop ECG was already present			

subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
hypoxia, hypotens & ischaemic ECG changes during prolonged period of dissection			
subjects affected / exposed	0 / 60 (0.00%)	1 / 30 (3.33%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
ST changes after removal of cross clamp, visible air in coronaries			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
bowel perforation on insertion of PD cath			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Surgical and medical procedures			
tear or abrasion to stomach on PD cath insertion			
subjects affected / exposed	0 / 60 (0.00%)	3 / 30 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	3	0
inominate vein punctured during CVC insertion			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
mediastinal wash out as bleeding concerns, antiXa supratherapeutic			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
insufficient heparinisation, low AT3, AT3 conc. given			
subjects affected / exposed	0 / 60 (0.00%)	1 / 30 (3.33%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
pulm. haemorrh & difficult ventil on PICU adm.			
subjects affected / exposed	0 / 60 (0.00%)	1 / 30 (3.33%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
pulmonary haemorrhage			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0

tension pneumothorax			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Pleural Effusion			
subjects affected / exposed	1 / 60 (1.67%)	0 / 30 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
hypoxia after coming off bypass			
subjects affected / exposed	2 / 60 (3.33%)	0 / 30 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported