Clinical trial results:
Pilot Randomized trial of Fibrinogen in Trauma Haemorrhage (PRooF-iTH).

Summary

EudraCT number	2014-003978-16
Trial protocol	DK
Global end of trial date	15 November 2016

Results information

Result version number	v1 (current)
This version publication date	28 May 2022
First version publication date	28 May 2022

Trial information

Trial identification

Sponsor protocol code	PRooF-iTH

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02344069
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Rigshospitalet, Section for Transfusion Medicine, Capitol Region Blood Bank
Sponsor organisation address	Blegdamsvej 9, Copenhagen, Denmark, DK-2100
Public contact	Jakob Stensballe, Section for Transfusion Medicine, Capitol Region Blood Bank, 45 35458587, jakob.stensballe@regionh.dk
Scientific contact	Jakob Stensballe, Section for Transfusion Medicine, Capitol Region Blood Bank, 45 35458587, jakob.stensballe@regionh.dk

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	15 November 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 November 2016
Global end of trial reached?	Yes
Global end of trial date	15 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective is to assess the efficacy and safety of an immediate pre-emptive first-line treatment with fibrinogen concentrate in patients with trauma haemorrhage in need of haemostatic resuscitation.

Protection of trial subjects:

All patients are included upon admission to the trauma center and is receiving the best possible care and monitoring to treat their injury.
The dose of fibrinogen concentrate in the present trial is 60-70 mg/kg and this is in alignment with the recommended dose stated in the summary of product characteristics (SPC) from CSL Behring

Background therapy:

Standard of care at the trauma center

Evidence for comparator: -

Actual start date of recruitment	15 November 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 46
Worldwide total number of subjects	46
EEA total number of subjects	46

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)	42
From 65 to 84 years	2
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Patient were recruited upon admisssion to the trauma center at Rigshospitalet. Informed consent were obtained by an independed scientific guardian before inclusion in the trail. Afterwards informed consent is obtained from next of kin and/or the patient when able to concent.

Pre-assignment

Screening details:

A this i an emergency trial, patients were screening for inclusion immediatly after arrival to the trauma center. The primary inclusion criteria are: age at 18 or above, requiring blood transfusion,

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

Blinding implementation details:

This is a single-centre, randomized (1:1, active:placebo), placebo-controlled, double-blinded trial.
The randomization is done in blocks of six, and the randomization sequence and envelopes are generated and validated by two persons that are otherwise not involved in the trial. Randomization was performed using Microsoft Excel software.
Two identical sets of envelopes are generated - one set for randomization of patients, and an "emergency" set for code breaking if necessary.

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention arm

Arm description:

The active treatment consists of intravenous injection of fibrinogen concentrate (Riastap®) of 60–70 mg/kg (dose of 4 g for patients with body weight 55–69 kg, 5 g for 70–85 kg or 6 g for >85 kg) as a bolus dose when haemostatic resuscitation is deemed necessary by the clinician. Fibrinogen is administered as an immediate single intravenous injection (bolus dose) as early as possible during the initial resuscitation.

Arm type	Experimental
Investigational medicinal product name	Riastap
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Riastap® is given as a intervenous bolus dose of 60–70 mg/kg (dose of 4 g for patients with body weight 55–69 kg, 5 g for 70–85 kg or 6 g for >85 kg)

Arm title	Placebo arm

Arm description:

Patients in the placebo group will receive 0.9 % saline infusions in equal volume to active treatment and will be treated exactly as active patients.
The volume of placebo administered is equal to the volume of active drug administered, again as a bolus dose when haemostatic resuscitation is deemed necessary by the clinician.

Arm type	Placebo

Investigational medicinal product name	Saline 0.9%
Investigational medicinal product code	
Other name	sodium chloride
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients in the placebo group will receive 0.9 % saline infusions in equal volume to active treatment and will be treated exactly as active patients. The volume of placebo administered is equal to the volume of active drug administered

Number of subjects in period 1	Intervention arm	Placebo arm
Started	23	23
Completed	21	19
Not completed	2	4
Died before intervention	-	1
No need for blood transfusion	1	-
Missed allokation	-	1
Protocol deviation	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Intervention arm

Reporting group description:

The active treatment consists of intravenous injection of fibrinogen concentrate (Riastap®) of 60–70 mg/kg (dose of 4 g for patients with body weight 55–69 kg, 5 g for 70–85 kg or 6 g for >85 kg) as a bolus dose when haemostatic resuscitation is deemed necessary by the clinician. Fibrinogen is administered as an immediate single intravenous injection (bolus dose) as early as possible during the initial resuscitation.

Reporting group title	Placebo arm

Reporting group description:

Patients in the placebo group will receive 0.9 % saline infusions in equal volume to active treatment and will be treated exactly as active patients.
The volume of placebo administered is equal to the volume of active drug administered, again as a bolus dose when haemostatic resuscitation is deemed necessary by the clinician.

Reporting group values	Intervention arm	Placebo arm	Total
Number of subjects	23	23	46
Age categorical			
all patients at 18 or above is eligiable			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	20	22	42
From 65-84 years	2	0	2
85 years and over	1	1	2
Gender categorical			
Both men and women were incluted			
Units: Subjects			
Female	3	4	7
Male	20	19	39

End points

End points reporting groups

Reporting group title	Intervention arm

Reporting group description:

The active treatment consists of intravenous injection of fibrinogen concentrate (Riastap®) of 60–70 mg/kg (dose of 4 g for patients with body weight 55–69 kg, 5 g for 70–85 kg or 6 g for >85 kg) as a bolus dose when haemostatic resuscitation is deemed necessary by the clinician. Fibrinogen is administered as an immediate single intravenous injection (bolus dose) as early as possible during the initial resuscitation.

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The volume of placebo administered is equal to the volume of active drug administered, again as a bolus dose when haemostatic resuscitation is deemed necessary by the clinician.

Primary: Thrombelastograph (TEG) functional fibrinogen (FF)

End point title	Thrombelastograph (TEG) functional fibrinogen (FF)

End point description:

Primary endpoint is thrombelastograph (TEG) functional fibrinogen (FF) maximun amplitude (MA) at 15 minuts after the intervention
TEG FF MA ws significant higher in the fibrinogen group as compared to placebo (P<0.00001)

End point type	Primary

End point timeframe:

15 minuts after the intervention

End point values	Intervention arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: mm				
median (inter-quartile range (Q1-Q3))				
FF MA	24 (23 to 26)	19 (16 to 22)		

Statistical analyses

Statistical analysis title	Primary endpoint

Statistical analysis description:

TEG FF MA at 15 min was significant higher in the fibrinogen group as compared to the placebo group

Comparison groups	Intervention arm v Placebo arm

Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.05 [2]
Method	ANCOVA
Parameter estimate	Cox proportional hazard

Notes:

[1] - Numeric variable was presented as medians with interquartile range analysed by Mann-Whitney U test
[2] - Primary endpoint were analysed with ANCOVA, adjusted for baseline values to increase statistical power

Secondary: Mortality at 24 hours

End point title	Mortality at 24 hours

End point description:

ITT population
Number of death within 24-hours post intervention.
There were no statistical difference between the groups.

End point type	Secondary

End point timeframe:

"4 hours post intervention

End point values	Intervention arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	19		
Units: number				
Death	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Mortality day 30

End point title	Mortality day 30

End point description:

ITT population
Numbers of deaths from baseline to day 30
There were no statistical difference between the groups.

End point type	Secondary

End point timeframe:

Day 30

End point values	Intervention arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	19		
Units: numbers				
Death	4	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Transfusion requirements

End point title	Transfusion requirements

End point description:

ITT population
The transfusion requirements in the fibrinogen group was significant lower in the first 2 hours after the intervention (p=0.048)

End point type	Secondary

End point timeframe:

at 2 hours post intervention

End point values	Intervention arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: units				
median (inter-quartile range (Q1-Q3))				
Transfusion units	2 (1 to 4)	5 (3 to 13)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Adverse events are collected from baseline to day 30. Only SAE and SAR are recorded in the study as these patients are severily ill upon admission to the trauma center

Assessment type	Systematic

Dictionary used

Dictionary name	none
Dictionary version	0

Reporting groups

Reporting group title	Overall trail

Reporting group description: -

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: AE and AR is not reported in this trial as this trial is in trauma patients which per definition are seriously ill and therefore will have several AE without any value for the safety reporting in this trial

Serious adverse events	Overall trail		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 46 (8.70%)		
number of deaths (all causes)	9		
number of deaths resulting from adverse events	0		
Vascular disorders			
Trombose	Additional description: 4 events of trombosis were seen (1 of 23 in the fibrinogen group and 3 of 23 in the placebo group)		
subjects affected / exposed	4 / 46 (8.70%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Overall trail		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 46 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 February 2016	Extension of trial period

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported