Clinical trial results:
A multicenter double-blind, placebo controlled, randomized, pilot trial to assess the efficacy of pre-hospital administration of Fibrinogen Concentrate (FGTW) in trauma patients, presumed to bleed (FI in TIC)

Summary

EudraCT number	2010-022923-31
Trial protocol	AT DE CZ
Global end of trial date	18 November 2015

Results information

Result version number	v1 (current)
This version publication date	10 September 2021
First version publication date	10 September 2021
Summary attachment (see zip file)	FINTIC Publication in EJA 2021 (ejanet-38-348.pdf)

Trial information

Trial identification

Sponsor protocol code	FIinTIC

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01475344
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medical Universität of Innsbruck
Sponsor organisation address	Anichstrasse 35, Insnbruck, Austria,
Public contact	Clinical Trial Office Dr. Fries, Medical University of Innsbruck, 0043 0512504 80451, mirjam.bachler@i-med.ac.at
Scientific contact	Clinical Trial Office Dr. Fries, Medical University of Innsbruck, 0043 0512504 80451, mirjam.bachler@i-med.ac.at

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 January 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 November 2015
Global end of trial reached?	Yes
Global end of trial date	18 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To asses whether the ultra-early pro-coagulatory treatment with fibrinogen concentrate on the scene would improve plasmatic coagulation capacity in multiple trauma patients with bleeding and/or major blood loss.

Protection of trial subjects:

To protect the trial subjects the study was conducted in compliance with Good Clinical Practices, the Declaration of Helsinki in its latest version, the local laws and regulations and the applicable regulatory requirements. An on-site monitoring was set up to check the safety of patients.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 August 2011
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	Austria: 61
Country: Number of subjects enrolled	Czechia: 2
Country: Number of subjects enrolled	Germany: 4
Worldwide total number of subjects	67
EEA total number of subjects	67

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)	56
From 65 to 84 years	11

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The recruitment was planned to last until 60 (2x30) evaluable patients will be included. The global recruitment process started in August 2011 in Tyrol, Austria with the Center Christophorus 1 and Medical University of Innsbruck. In August 2013 the centers in Germany and in June 2015 the centers in the Czech Republic were initiated.

Pre-assignment

Screening details:

Severely injured patients aged at least 18 years with major bleeding and need for volume replacement therapy were screened and enrolled by experienced emergency physicians at the scene of trauma. Admission to one of the study trauma centres was required to ensure adhere to the study protocol.

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

Blinding implementation details:

The placebo was also designed to have the same physical form (powder) as fibrinogen concentrate. FGTW and placebo were packaged in the same type of vials and boxes to preserve the double-blinding. The packaging for one patient is calculated for a maximum weight of 120 kg.

Arms

Are arms mutually exclusive?	Yes
Arm title	Fibrinogen concentrate

Arm description:

Patients allocated to the fibrinogen group received 50 mg/kg Body Weight fibrinogen concentrate (one 100 ml vial of 1.5 g of fibrinogen for each 30 kg body weight, estimated by the emergency physician).

Arm type	Experimental
Investigational medicinal product name	Fibrinogen concentrate
Investigational medicinal product code	FGTW
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The study drug dose was 1.5 g per 30 kg of estimated body weight to achieve the recommended dosage of 50 mg/kg. To enable the administration of the recommended dosage, the patients were stratified by the emergency physician into different body weight groups (30-kg steps). A dose of 3 g of the study drug was given in patients with bodyweight 30 to 60 kg, 4.5 g in patients with bodyweight 60 to 90 kg and 6 g in patients with bodyweight 90 to 120 kg. For all patients weighing 120 kg or more, the dose was still 6 g because blood volume increases only slightly with increasing obesity. Each 1.5 g of powder was reconstituted in 100 ml of solvent. The study drug was administered via an intravenous infusion at a rate of 20 ml/min, either at the scene of trauma or during transportation to the participating hospital.

Arm title	Placebo

Arm description:

Patients allocated to the placebo group received 50 mg/kg Body Weight placebo powder (one 100 ml vial of 1.5 g of fibrinogen for each 30 kg body weight, estimated by the emergency physician).

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The placebo dose was 1.5 g per 30 kg of estimated body weight to achieve the recommended dosage of 50 mg/kg. To enable the administration of the recommended dosage, the patients were stratified by the emergency physician into different body weight groups (30-kg steps). A dose of 3 g of the placebo was given in patients with bodyweight 30 to 60 kg, 4.5 g in patients with bodyweight 60 to 90 kg and 6 g in patients with bodyweight 90 to 120 kg. For all patients weighing 120 kg or more, the dose was still 6 g because blood volume increases only slightly with increasing obesity. Each 1.5 g of powder was reconstituted in 100 ml of solvent. The placebo was administered via an intravenous infusion at a rate of 20 ml/min, either at the scene of trauma or during transportation to the participating hospital.

Number of subjects in period 1	Fibrinogen concentrate	Placebo
Started	37	30
Completed	37	30

Baseline characteristics

Reporting groups	
Reporting group title	Fibrinogen concentrate
Reporting group description:	
Patients allocated to the fibrinogen group received 50 mg/kg Body Weight fibrinogen concentrate (one 100 ml vial of 1.5 g of fibrinogen for each 30 kg body weight, estimated by the emergency physician).	
Reporting group title	Placebo
Reporting group description:	
Patients allocated to the placebo group received 50 mg/kg Body Weight placebo powder (one 100 ml vial of 1.5 g of fibrinogen for each 30 kg body weight, estimated by the emergency physician).	

Reporting group values	Fibrinogen concentrate	Placebo	Total
Number of subjects	37	30	67
Age categorical			
In the verum group 32 persons fell in the age category minimum 18 years or more and maximum 64 years whereas 5 persons were older than 65 years. In the placebo group 24 persons were between 18 and 64 years old and 6 persons older than 64 years. In the verum as well as in the placebo group each a persons age was unknown and estimated with 18 years. Since these patients were lost to follow up after the termination of the treatment, the real age could not be determined. Therefore these tw patients were left out in the age analysis and were not included in the final analysis data set.			
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)	32	24	56
From 65-84 years	5	6	11
85 years and over	0	0	0
Age continuous			
In the verum group the median age was 46 years and in the placebo group 50 years. There is no statistical difference between these to groups (p=0.800).			
Units: years			
median	46	50	
inter-quartile range (Q1-Q3)	34 to 58	37 to 56	-
Gender categorical			
Units: Subjects			
Female	6	5	11
Male	31	25	56
Fibrinogen levels before IMP administration			
Units: mg/dl			
median	244	234	
inter-quartile range (Q1-Q3)	171 to 267	206 to 259	-
ROTEM FIBTEM MCF before IMP administration			
Units: mm			
median	13	13	

inter-quartile range (Q1-Q3)	9 to 17	10 to 15	-

Subject analysis sets

Subject analysis set title	Full analysis
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All analyses were conducted in the modified intention-to-treat (ITT) population, that is all patients receiving fibrinogen concentrate or placebo in whom posttreatment assessment of FIBTEM MCF was available and all inclusion/exclusion criteria were fullfilled at re-check of the criteria in the hospital. After randomisation, four patients in the fibrinogen concentrate group and three patients in the placebo group were withdrawn from the study due to previously undetected fulfilment of exclusion criteria. A further seven patients (five from the fibrinogen concentrate arm and two from the placebo arm) were excluded due to missing data for the primary endpoint. Thus, the modified ITT population comprised 28 patients in the fibrinogen concentrate arm and 25 patients in the placebo arm.

Reporting group values	Full analysis		
Number of subjects	53		
Age categorical			
In the verum group 32 persons fell in the age category minimum 18 years or more and maximum 64 years whereas 5 persons were older than 65 years. In the placebo group 24 persons were between 18 and 64 years old and 6 persons older than 64 years. In the verum as well as in the placebo group each a persons age was unknown and estimated with 18 years. Since these patients were lost to follow up after the termination of the treatment, the real age could not be determined. Therefore these tw patients were left out in the age analysis and were not included in the final analysis data set.			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	44		
From 65-84 years	9		
85 years and over	0		
Age continuous			
In the verum group the median age was 46 years and in the placebo group 50 years. There is no statistical difference between these to groups (p=0.800).			
Units: years			
median	49		
inter-quartile range (Q1-Q3)	35 to 58		
Gender categorical			
Units: Subjects			
Female	9		
Male	44		
Fibrinogen levels before IMP administration			
Units: mg/dl			
median	242		
inter-quartile range (Q1-Q3)	206 to 266		
ROTEM FIBTEM MCF before IMP administration			

Units: mm			
median	13		
inter-quartile range (Q1-Q3)	9 to 15		

End points

End points reporting groups

Reporting group title	Fibrinogen concentrate

Reporting group description:

Patients allocated to the fibrinogen group received 50 mg/kg Body Weight fibrinogen concentrate (one 100 ml vial of 1.5 g of fibrinogen for each 30 kg body weight, estimated by the emergency physician).

Reporting group title	Placebo

Reporting group description:

Patients allocated to the placebo group received 50 mg/kg Body Weight placebo powder (one 100 ml vial of 1.5 g of fibrinogen for each 30 kg body weight, estimated by the emergency physician).

Subject analysis set title	Full analysis
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All analyses were conducted in the modified intention-to-treat (ITT) population, that is all patients receiving fibrinogen concentrate or placebo in whom posttreatment assessment of FIBTEM MCF was available and all inclusion/exclusion criteria were fullfilled at re-check of the criteria in the hospital. After randomisation, four patients in the fibrinogen concentrate group and three patients in the placebo group were withdrawn from the study due to previously undetected fulfilment of exclusion criteria. A further seven patients (five from the fibrinogen concentrate arm and two from the placebo arm) were excluded due to missing data for the primary endpoint. Thus, the modified ITT population comprised 28 patients in the fibrinogen concentrate arm and 25 patients in the placebo arm.

Primary: Fibrinogen polymerisation measure with the FIBTEM MCF at V2

End point title	Fibrinogen polymerisation measure with the FIBTEM MCF at V2

End point description:

End point type	Primary

End point timeframe:

ROTEM FIBTEM MCF measurements at visit 2 (emergency department after termination of the IMP administration).

End point values	Fibrinogen concentrate	Placebo	Full analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	28[1]	25[2]	53	
Units: mm				
median (inter-quartile range (Q1-Q3))	16 (12 to 18)	10 (8 to 14)	13 (10 to 17)	

Notes:

[1] - Modified ITT population is used

[2] - Modified ITT population is used

Statistical analyses

Statistical analysis title	Statistical assessment of primary endpoint

Statistical analysis description:

Initial analysis of the FIBTEM MCF results (Shapiro--Wilk normality test) showed that the data were not normally distributed. A revised sample size calculation, based on the observed changes in FIBTEM MCF, implied that 20 patients per group would be sufficient to detect a 1mm difference in FIBTEM MCF change with a power of 80%. The Wilcoxon rank sum test was used to assess between-group and within-group differences in FIBTEM MCF.

Comparison groups	Fibrinogen concentrate v Placebo

Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: Fibrinogen levels (Clauss) at V2

End point title	Fibrinogen levels (Clauss) at V2

End point description:

End point type	Secondary

End point timeframe:

Fibrinogen levels (mg/dl) at visit 2 (emergency department after termination of the IMP administration).

End point values	Fibrinogen concentrate	Placebo	Full analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	28	25	53	
Units: mg/dl				
median (inter-quartile range (Q1-Q3))	264 (220 to 338.5)	178 (149 to 240)	240 (170 to 288)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events:	
All adverse events, regardless of relationship or seriousness were recorded from IMP administration until the visit T7 at day 7 (half-life of FGTW is 3.5 days).	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15

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

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: Since these were critically ill patients, the reported non-serious adverse events were too numerous to list them in the full data set. Three (5.7%) thromboembolic complications occurred within 7 days after the administration of the study drug. Two thromboembolic events were detected in patients who had received fibrinogen concentrate and one event in patients who received placebo. The difference was not significant.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 December 2013	- Inclusion criterion I.3.: Removal of "with parameters of shock" since many patients don´t show parameters of shock when the emergency physician arrives at the scene of accident - Exclusion criterion E.1: Change from "Penetrating trauma" to "Solely penetrating trauma" to clarify that polytrauma patients with also a penetrating trauma can be included. - Exclusion criterion E.3: Ongoing hemodynamic instability was simpler defined.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported