



## Clinical trial results:

**A prospective, controlled, randomised, cross-over study investigating the pharmacokinetic properties, surrogate efficacy and safety of Octafibrin compared to Haemocomplettan® P/ RiaSTAP™ in subjects with congenital fibrinogen deficiency**

### Summary

EudraCT number	2011-002403-15
Trial protocol	GB DE IT
Global end of trial date	19 January 2015

### Results information

Result version number	v1 (current)
This version publication date	31 July 2016
First version publication date	31 July 2016

### Trial information

#### Trial identification

Sponsor protocol code	Forma-01
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01575756
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Octapharma AG
Sponsor organisation address	Seidenstrasse 2, Lachen, Switzerland, CH-8853
Public contact	Clinical Research and Development, Octapharma Pharmazeutika Produktionsgesellschaft m.b.H, 0043 1610320, clinical.department@octapharma.com
Scientific contact	Clinical Research and Development, Octapharma Pharmazeutika Produktionsgesellschaft m.b.H, 0043 1610320, clinical.department@octapharma.com

Notes:

### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-001208-PIP01-11
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	14 August 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	19 January 2015
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

- To determine the single dose pharmacokinetics of Octafibrin and Haemocomplettan® P/RiaSTAPTM in subjects with congenital fibrinogen deficiency
- To determine maximum clot strength (maximum clot firmness [MCF]) as a surrogate marker for haemostatic efficacy before and after administration of Octafibrin and Haemocomplettan® P/ RiaSTAPTM in subjects with congenital fibrinogen deficiency.

Protection of trial subjects:

This trial was conducted in accordance to the principles of GCP, ensuring that the rights, safety and well-being of patients are protected and in consistency with the the Declaration of Helsinki. Inclusion and exclusion criteria were carefully defined in order to protect subjects from contraindications, interactions with other medication and safety factors associated with the investigational medicinal product.

Throughout the study safety was assessed, such as occurrence of AEs, labvalues, vital signs and physical examinations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 June 2013
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	United Kingdom: 3
Country: Number of subjects enrolled	Bulgaria: 1
Country: Number of subjects enrolled	India: 8
Country: Number of subjects enrolled	Iran, Islamic Republic of: 7
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	United States: 2
Worldwide total number of subjects	22
EEA total number of subjects	4

Notes:

### Subjects enrolled per age group

In utero	0
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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)	6
Adults (18-64 years)	16
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details: -

### Pre-assignment period milestones

Number of subjects started	22
Number of subjects completed	22

### Period 1

Period 1 title	overall trial
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Octafibrin Followed by Haemocomplettan® P or RiaSTAPTM

Arm description:

Participants received a single dose of Octafibrin 70 mg/kg intravenously once followed by Haemocomplettan® P or RiaSTAPTM 70 mg/kg intravenously 45 days later or Haemocomplettan® P or RiaSTAPTM 70 mg/kg intravenously followed by Octafibrin 70 mg/kg intravenously 45 days later in a randomized crossover design

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

Dosage and administration details:

Octafibrin is a human plasma-derived fibrinogen concentrate for intravenous use. The product was packed and labelled according to local regulations in vials containing 1 g of lyophilised fibrinogen concentrate powder for reconstitution with 50 mL of water for injection (WFI). Octafibrin was administered at a dose of 70 mg/kg body weight (BW). It was administered as an intravenous bolus injection at a maximum speed of 5 mL/min. (based on the labelled potency).

Investigational medicinal product name	Haemocomplettan® P/RiaSTAPTM
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

The reference therapy in this study was Haemocomplettan® P/RiaSTAPTM, which is a marketed fibrinogen concentrate. It was administered intravenously at a dose of 70 mg/kg BW (based on the labelled potency).

<b>Arm title</b>	Haemocomplettan® P or RiaSTAPTM Followed by Octafibrin
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Arm description:

Participants received a single dose of Haemocomplettan® P or RiaSTAPTM 70 mg/kg intravenously in a randomized crossover design followed by Octafibrin 70 mg/kg intravenously 45 days later.

Arm type	Experimental
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Investigational medicinal product name	Haemocomplettan® P/RiaSTAPTM
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

**Dosage and administration details:**

The reference therapy in this study was Haemocomplettan® P/RiaSTAPTM, which is a marketed fibrinogen concentrate. It was administered intravenously at a dose of 70 mg/kg BW (based on the labelled potency).

Investigational medicinal product name	Octafibrin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous use

**Dosage and administration details:**

Octafibrin is a human plasma-derived fibrinogen concentrate for intravenous use. The product was packed and labelled according to local regulations in vials containing 1 g of lyophilised fibrinogen concentrate powder for reconstitution with 50 mL of water for injection (WFI). Octafibrin was administered at a dose of 70 mg/kg body weight (BW). It was administered as an intravenous bolus injection at a maximum speed of 5 mL/min. (based on the labelled potency).

<b>Number of subjects in period 1</b>	Octafibrin Followed by Haemocomplettan® P or RiaSTAPTM	Haemocomplettan® P or RiaSTAPTM Followed by Octafibrin
Started	11	11
Completed	11	11

**Period 2**

Period 2 title	Octafibrin
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

**Arms**

<b>Arm title</b>	Octafibrin
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Octafibrin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous use

**Dosage and administration details:**

Octafibrin is a human plasma-derived fibrinogen concentrate for intravenous use. The product was packed and labelled according to local regulations in vials containing 1 g of lyophilised fibrinogen

concentrate powder for reconstitution with 50 mL of water for injection (WFI). Octafibrin was administered at a dose of 70 mg/kg body weight (BW) It was administered as an intravenous bolus injection at a maximum speed of 5 mL/min.(based on the labelled potency).

<b>Number of subjects in period 2</b>	Octafibrin
Started	22
Completed	22

### Period 3

Period 3 title	Haemocomplettan® P or RiaSTAPTM
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

### Arms

<b>Arm title</b>	Haemocomplettan® P or RiaSTAPTM
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Haemocomplettan® P/RiaSTAPTM
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

#### Dosage and administration details:

The reference therapy in this study was Haemocomplettan® P/RiaSTAPTM, which is a marketed fibrinogen concentrate. It was administered intravenously at a dose of 70 mg/kg BW (based on the labelled potency).

<b>Number of subjects in period 3</b>	Haemocomplettan® P or RiaSTAPTM
Started	22
Completed	22



## Baseline characteristics

### Reporting groups

Reporting group title	overall trial
Reporting group description: -	

Reporting group values	overall trial	Total	
Number of subjects	22	22	
Age categorical			
Units: Subjects			
< 18 years	6	6	
>= 18-65 years	16	16	
Age continuous			
Units: years			
arithmetic mean	26		
full range (min-max)	12 to 53	-	
Gender categorical			
Units: Subjects			
Female	15	15	
Male	7	7	

### Subject analysis sets

Subject analysis set title	PK Analysis Set (PK-PP)
Subject analysis set type	Per protocol

Subject analysis set description:

The PK analysis set will include all patients who completed the PK assessment per protocol (PP)

Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set, defined according to the intention-to-treat (ITT) principle, will include all randomized patients who received at least one infusion of study medication (Octafibrin and/or any part of an infusion of Haemocomplettan® P/ RiaSTAP™) and for whom any post-treatment data is available.

Reporting group values	PK Analysis Set (PK-PP)	Full Analysis Set (FAS)	
Number of subjects	21	22	
Age categorical			
Units: Subjects			
< 18 years	5	6	
>= 18-65 years	16	16	
Age continuous			
Units: years			
arithmetic mean	26.6	26	
full range (min-max)	12 to 53	12 to 53	
Gender categorical			
Units: Subjects			
Female	14	15	
Male	7	7	





## End points

### End points reporting groups

Reporting group title	Octafibrin Followed by Haemocomplettan® P or RiaSTAPTM
Reporting group description: Participants received a single dose of Octafibrin 70 mg/kg intravenously once followed by Haemocomplettan® P or RiaSTAPTM 70 mg/kg intravenously 45 days later or Haemocomplettan® P or RiaSTAPTM 70 mg/kg intravenously followed by Octafibrin 70 mg/kg intravenously 45 days later in a randomized crossover design	
Reporting group title	Haemocomplettan® P or RiaSTAPTM Followed by Octafibrin
Reporting group description: Participants received a single dose of Haemocomplettan® P or RiaSTAPTM 70 mg/kg intravenously in a randomized crossover design followed by Octafibrin 70 mg/kg intravenously 45 days later.	
Reporting group title	Octafibrin
Reporting group description: -	
Reporting group title	Haemocomplettan® P or RiaSTAPTM
Reporting group description: -	
Subject analysis set title	PK Analysis Set (PK-PP)
Subject analysis set type	Per protocol
Subject analysis set description: The PK analysis set will include all patients who completed the PK assessment per protocol (PP)	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description: The full analysis set, defined according to the intention-to-treat (ITT) principle, will include all randomized patients who received at least one infusion of study medication (Octafibrin and/or any part of an infusion of Haemocomplettan® P/ RiaSTAPTM) and for whom any post-treatment data is available.	

### Primary: Fibrinogen Activity Normalized Area Under the Curve Standardized

End point title	Fibrinogen Activity Normalized Area Under the Curve Standardized <sup>[1]</sup>
End point description: Fibrinogen activity was determined via a validated Clauss assay (fibrinogen activity) and fibrinogen-specific enzyme-linked immunosorbent assay (ie, fibrinogen antigen) using paired antibodies for fibrinogen antigen. All determinations were performed on frozen plasma samples in a central laboratory. The Clauss assay was modified and validated to achieve a limit of quantification of 0.2 g/L. The pharmacokinetic analysis was assessed individually using a non-compartmental model. Plasma levels were measured at Baseline, 0.5, 1, 2, 4, 8, 24, 48, 96, 144, 216, and 312 hours post-treatment. The normalized area under the curve was standardized to a dose of 70 mg/kg.	
End point type	Primary
End point timeframe: Blood samples for the PK assessments were taken over a period of 14 days at baseline, 0.5, 1, 2, 4, 8, 24, 48, 96, 144, 216 and 312 hours post-infusion	
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: The pharmacokinetic analysis was assessed individually using a non-compartmental model. Plasma levels were measured at Baseline, 0.5, 1, 2, 4, 8, 24, 48, 96, 144, 216, and 312 hours post-treatment. The normalized area under the curve was standardized to a dose of 70 mg/kg. Because of the cross over design the statistical analyses of this endpoint is already reported as Fibrinogen Activity Normalized AUC.	

End point values	Octafibrin	Haemocompletan® P or RiaSTAPTM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	21		
Units: g•h/L				
arithmetic mean (confidence interval 95%)	113.7 (101.96 to 124.55)	96.39 (84.006 to 108.76)		

## Statistical analyses

No statistical analyses for this end point

## Primary: Change in Maximum Clot Firmness 1 Hour Post-treatment From Baseline

End point title	Change in Maximum Clot Firmness 1 Hour Post-treatment From Baseline <sup>[2]</sup>
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End point description:

Thromboelastometry (ROTEM®) was used to measure maximum clot firmness. Thromboelastometry is a method for the continuous measurement of clot formation. Maximum clot firmness is a functional parameter that depends on the activation of coagulation, the platelet and fibrinogen content of the blood sample, and the polymerisation and cross-linking of the fibrin network. In order to obtain comparable results from all study centres, maximum clot firmness data were assessed from frozen citrated plasma samples in a central laboratory. As these samples did not contain platelets that would be found in the whole blood assay, only the fibrinogen content defined the maximum clot firmness.

End point type	Primary
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End point timeframe:

baseline and 1 hour post-infusion

Notes:

[2] - 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: For each time point and treatment group, the mean, SD, median and range has been provided for the absolute MCF values and the changes from baseline (i.e. from pre-infusion). Mean changes in MCF between baseline and the 1 hour value have been described with two-sided 95% CIs based on the paired t-test. Further, the intra-individual differences between the changes from BL for each treatment will be described; corresponding 95% CI intervals based on the paired t-test was generated.

End point values	Octafibrin	Haemocompletan® P or RiaSTAPTM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: mm				
arithmetic mean (confidence interval 95%)	9.68 (8.37 to 10.99)	10 (8.07 to 11.93)		

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AEs occurring from Day 1 up to Day 14 post administration in each study period and SAEs occurring from Day 1 to Day 45 in each study period

Adverse event reporting additional description:

Treatment-emergent adverse events (TEAEs) were defined as AEs occurring from Day 1 up to Day 14 post administration in each study period. Additionally, SAEs were considered TEAEs from Day 1 in first study period until study completion on day 45

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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### Reporting groups

Reporting group title	Octafibrin
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Reporting group description:

AEs occurring from Day 1 up to Day 14 post administration in each study period and SAEs occurring from Day 1 to Day 45 in each study period.

Reporting group title	Haemocomplettan® P/RiaSTAPTM
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Reporting group description:

AEs occurring from Day 1 up to Day 14 post administration in each study period and SAEs occurring from Day 1 to Day 45 in each study period.

Serious adverse events	Octafibrin	Haemocomplettan® P/RiaSTAPTM	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Vaginal Haemorrhage			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

<b>Non-serious adverse events</b>	Octafibrin	Haemocomplettan® P/RiaSTAPTM	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 22 (9.09%)	5 / 22 (22.73%)	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 22 (0.00%)	2 / 22 (9.09%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 22 (9.09%)	3 / 22 (13.64%)	
occurrences (all)	2	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 22 (9.09%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
Pain in extremity			
subjects affected / exposed	1 / 22 (4.55%)	2 / 22 (9.09%)	
occurrences (all)	1	2	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 22 (4.55%)	2 / 22 (9.09%)	
occurrences (all)	1	2	

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported